ARCHIVES of INTERNAL MEDICINE

VOLUME 61 FEBRUARY 1938 NUMBER 2

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FATAL RHEUMATIC FEVER

EDWARD F. BLAND, M.D.
AND
T. DUCKETT JONES, M.D.
BOSTON

We present in this report clinical observations on the fatal course of rheumatic fever and its sequelae in 306 young patients. Our purpose is twofold. First, there are important aspects of the natural course of the disease which are best displayed by this special group, and, second, certain clinical features which characterize the disease in its more severe form are not generally recognized as important manifestations of rheumatic fever. The significance of these less well recognized manifestations becomes increasingly evident from a consideration of these fatalities.

MATERIAL

The material dealt with is in some respects unusual. During the past sixteen years (since 1921) approximately 1,500 children and adolescents under the age of 21 years have received prolonged care in bed at the House of the Good Samaritan during the course of active rheumatic fever and chorea. The subsequent course of these patients has been followed by frequent examinations and, when necessary, by readmission of the patients to the hospital. The present status of this large group is known. The 306 patients who are the subject of this report constitute those who have died during the course of the study. We are especially concerned, however, with the 250 fatalities directly attributable to rheumatic fever.

Although it is not our purpose to discuss these fatal cases in relation to the entire clinical group, it is of some interest to note at this time that the first 1,000 of the total of 1,500 patients have now been observed for an average period of more than ten years. The present status of this special group is as follows: Of these 1,000 patients, 310 have no demonstrable cardiac damage, 426 have varying degrees of residual rheumatic heart disease, 243 are dead (and comprise the major part of the present study) and finally there remain 21 patients whose present status is unknown. We are convinced that conclusions based on this and similar "average" (and hence incomplete) after-history studies of the course of a disease as notoriously variable as is rheumatic fever are unreliable other than as an indication,

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From the House of the Good Samaritan.

The expenses of this study have been defrayed by a grant from the Commonwealth Fund.

Presented at the meeting of the American Association for the Study and Control of Rheumatic Diseases, Atlantic City, N. J., June 7, 1937.

in its broadest sense, of the general trend of events. We propose to present later, as soon as the bulk of our observations permits, a detailed and final evaluation of the events which have occurred during each year of the first decade of the disease in these 1,000 patients. Until this information is available further statistical considerations can serve no useful purpose, nor can they be considered comparable to the completed ten year study recently reported by Grant [1] on the course of valvular heart disease in 1,000 men.

At this time we are concerned therefore with the incidence and significance of the factors responsible for the fatal outcome in the 306 patients. No patient has been included whose age at the onset of rheumatic fever (or chorea) exceeded 21 years, and the average age for the entire group was 8 years. It is to be emphasized that our observations are relevant only to the first ten years of the disease and embrace essentially the age period from 8 to 18 years, the decade during which rheumatic fever is most prevalent and most damaging to the heart.

TABLE 1.—*Causes of Death in 306 Fatal Cases*

		No. of Cases	Percentage
A. Rheumatic fever		250	82
Rheumatic fever and congestive failure	205		
Rheumatic fever	24		
Congestive failure	21		
B. Bacterial endocarditis		18	6
Acute	4		
Subacute	14		
C. Other causes related to heart		9	3
Sudden death	6		
Cerebral embolus	3		
D. Causes unrelated to heart		16	5
E. Causes unknown		13	4

DATA ON DEATHS

In table 1 we have indicated on the basis of clinical study the causes of death in the 306 fatal cases. The majority of the patients (140) died either at the House of the Good Samaritan or in a general hospital in Boston (85). The clinical notes thereby available render final judgment as to the cause of death reasonably accurate. Postmortem examination was made in 74 instances (24 per cent). In each case in which rheumatic infection had been considered the primary cause of death, the clinical impression was confirmed. Each of the remaining 68 patients for whom we have information relating to the final illness died at home under the care of the family physician. It should be noted that in 16 instances the cause of death was either accidental or irrelevant to our present study. There remain only 13 patients, who are known to be dead but for whom the details of whose final illness are too meager to permit reasonable deductions as to the responsible factors.

1. Grant, R. T.: After Histories for Ten Years of a Thousand Men Suffering from Heart Disease, Heart **6**:275 (June) 1933.

The outstanding cause of death has been rheumatic fever. It was directly responsible for the fatal issue in 250 instances (82 per cent) and was probably an important contributing factor in 19 additional instances.

COURSE OF EVENTS

In table 2 these 250 cases are arranged according to the years which elapsed from the appearance of the first recognizable symptoms of the disease to the time of death. Almost half the patients (47 per cent) succumbed during the first three years, and two thirds (62 per cent) of the fatalities occurred in the first five years. These figures assume increasing significance when it is recalled that the living counterpart of this group of deceased patients represents patients who have been followed for approximately ten years and in many instances well into the second decade of the disease. This feature of the natural course of rheumatic fever, so strikingly displayed by the group who died, is in agreement

TABLE 2.—*Duration of Rheumatic Fever from Onset to Death in 250 Cases*

	Duration, Years												
	1	2	3	4	5	6	7	8	9	10	11 to 15	16+	?
Number of cases	57	27	32	18	19	19	16	8	9	8	25	7	5
Percentage	23	11	13	7	8	8	6	3	3	3	10	3	2
Cumulative percentage	23	34	47	54	62	70	76	79	82	85	95	98	100
Age at onset	8.2	8.1	7.5	7.0	8.7	8.1	7.6	7.6	8.1	8.0	8.0	7.5	?

with concurrent observations (as yet unpublished) on the group of living patients. Here the importance of the first five years is also evident as the period beyond which reactivation, and hence progression of cardiac disease, is much less likely to occur.

In 94 per cent of our group of patients who died, representing the most unfavorable type of reaction (or disease), evidence of cardiac involvement was present from the onset of rheumatic fever. Furthermore, and perhaps of more fundamental importance, extensive cardiac enlargement occurred early and was noted at the time of the initial attack in all of those who died within the first year of the disease. Significant progression in valvular disease or an increase in the size of the heart with later attacks of rheumatic fever occurred in only 21 of the 153 patients who succumbed during the first five years.

These early years represent clearly a critical period which determines in large measure the future course of the disease. Thereafter the extent of residual cardiac enlargement (and to a lesser degree the rapidity with which it develops) serves as a reliable index of the original susceptibility of the patient's cardiac muscle to previous infection and indicates further its vulnerability to later recrudescences of

rheumatic activity. Grant has shown in his group of older patients (men) that the degree of functional cardiac limitation is directly related to the size of the heart. With this conception our data are in general agreement, except that in our group of considerably younger patients the dominant role of active rheumatic infection as the determining factor forces other considerations well into the background.

It is to be further noted in table 2 that there was no significant difference between the age at onset of those patients who succumbed to rheumatic fever within the first year of the disease and the age at onset of those who died after a longer period had elapsed. Furthermore, we have been unable to confirm, at least so far as longevity is concerned, the generally accepted impression that the younger the patient at the time of onset of rheumatic fever, the less favorable the subsequent course. The data in table 3 reveal no difference in the duration from onset to death in the patients whose disease began during the first five years as compared with the duration in those for whom

TABLE 3.—*Duration from Onset of Rheumatic Fever to Death*

	Age at Onset, Years				
	1 to 5	6 to 10	11 to 15	16+	?
Number of patients	61	132	36	16	5
Duration from onset to death, years	4.9	5.0	5.0	8.1	?

the onset dated from the second or third five year period. Our series contains too few patients (16) in whom the disease began after the age of 15 years to warrant the drawing of conclusions, yet the considerably longer duration of life in this small group agrees with our clinical impression and with the observations of others [2] that the age of puberty represents a second, and in this instance favorable, landmark in the natural course of the disease.

CLINICAL OBSERVATIONS

In certain important respects the clinical picture of severe, and in this group fatal, rheumatic fever differs profoundly from that represented by the earlier manifestations of the disease. It is frequently confused with the clinical picture of primary disease of the lungs (pneumonia), of the kidneys (acute nephritis) or of uncomplicated heart disease.

The fatal illness, the beginning of which was often poorly defined, we have called for convenience terminal. In the majority it represented an exacerbation of long-standing and clinically recognizable

2. Wilson, M. G.: The Natural History of Rheumatic Fever in the First Three Decades, J. Pediat. **10**:456 (April) 1937.

rheumatic fever. The duration of this so-called terminal illness usually extended over a period of months before the patient eventually succumbed to an exacerbation of toxic symptoms with increasing signs of heart failure. Less often the initial attack of rheumatic fever progressed to a fatal termination without a recognizable interval of significant improvement. In 4 of the patients showing the most rapidly fatal involvement the duration from the first appearance of symptoms of the disease to the time of death was three months, whereas in 25 additional patients death ensued within six months of the onset. In a few instances a fulminant recrudescence of apparently quiescent infection ended fatally in as short a period as ten days (chart).

TABLE 4.—*Clinical Manifestations of Rheumatic Fever During Final Illness in 250 Cases*

	No. of Cases	Percentage
I. Major manifestations (so-called)		
1. Arthritis	0	
2. Chorea	2	
3. Nodules (see text)	49	50
4. Carditis	250	100
A. Structural alterations		
a. Enlargement (dilatation)	250	100
b. Valvulitis (murmurs)	250	100
c. Pericarditis (friction rub)	47*	35
B. Functional manifestations		
a. Tachycardia	135*	100
b. Congestive failure	229	90
c. Delayed auriculoventricular conduction (electrocardiographic study in 83 cases)	33	40
d. Auricular fibrillation	45	18
II. Pulmonary signs		
1. Consolidation or pleurisy (friction rub)	38*	28
III. Hepatic signs		
1. Enlargement of liver	135*	100
2. Jaundice	4	

* On the basis of 135 patients who died of rheumatic fever at the House of the Good Samaritan.

It is beyond the scope of this report to review the more generally recognized manifestations of rheumatic fever other than to indicate certain features of the severe form which have been especially prominent in this group. The clinical picture prior to the fatal recrudescence is one of poor health, pallor, loss of weight, variable discomfort in the joints, muscles, chest and abdomen and often a low grade febrile reaction, with cyclic exacerbations. Superimposed on this ill defined syndrome of poor health in childhood or adolescence is a fairly characteristic group of symptoms and signs. Clinical observation and postmortem study have shown that they represent the manifestations of severe rheumatic fever. In table 4 these clinical features are arranged under three headings, as follows:

1. *Major Manifestations.*—In the first division we have indicated the incidence during the fatal illness of the four so-called major mani-

festations of rheumatic fever. This designation not only possesses some merit from established usage but is helpful in contrasting the symptoms and signs of severe rheumatic fever with the more generally recognized clinical picture of the disease. It is evident that important differences exist.

Arthritis: Arthritis, manifested by acutely painful, tender or swollen joints, was not present in any case during the course of the terminal illness. A history of arthritis, however, either at the onset of the original infection or with later recrudescences was common. Although arthritis

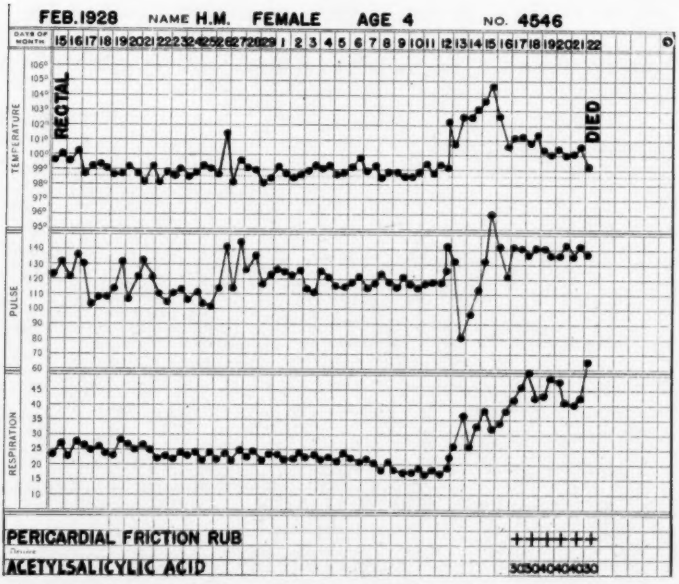

Chart showing a fulminant and fatal recrudescence of clinically quiescent rheumatic fever two weeks after an unexplained and transient elevation of temperature (J. Clin. Investigation **14**:633 [Sept.] 1935).

was absent, variable arthralgia causing sufficient discomfort to require salicylate therapy was observed in approximately half the group. It was never a prominent feature. Far more troublesome were abdominal and precordial pain, the latter occasionally requiring opiates for relief. The striking absence of arthritis and the relative mildness of articular manifestations in this group of patients with the most severe type of rheumatic fever need special emphasis. It is clear that if one fails to dissociate the two, the true nature of the severe form of the disease will be frequently overlooked.

Chorea: Chorea was rarely encountered. In only 2 patients was it present during the terminal illness, in both instances being manifested by a mild form of incoordination. In 53 (21 per cent) of the total group of 250 patients who died of rheumatic fever, chorea as a manifestation of rheumatic activity had been present during past illnesses, as compared with an incidence of 57 per cent for those still living. This further supports our previously expressed opinion that chorea is usually associated with a relatively mild form of rheumatic fever.[3] Chorea insaniens was not observed in the group of patients who died and has not been observed in those still living.

Subcutaneous Nodules: Subcutaneous nodules were present in 49 of the 83 patients (60 per cent) who have died at the House of the Good Samaritan since 1930. These structures are often found only after diligent search, being easily overlooked in a careful but otherwise routine examination. We have therefore based the incidence on the postmortem data for patients personally observed by us during the past six years. Rheumatic nodules appear to be of no prognostic significance other than with respect to their characteristic association with a severe and protracted form of the disease.

Carditis: Carditis was the only one of the four major manifestations present in every patient. Extensive and active involvement of the heart was manifested clinically by marked enlargement (dilatation), tachycardia, characteristic murmurs and ultimately failure of the congestive type. In a few instances of unusually fulminant rheumatic infection death ensued before the appearance of general venous engorgement. However, carditis was recognized clinically in 90 per cent of those who died of rheumatic fever.

The significance of the occurrence of congestive heart failure in patients with rheumatic heart disease during the first two decades of life, previously discussed by others,[4] is worthy of further emphasis. We have reason to believe it is not generally appreciated that heart failure in this age group is not primarily an expression of mechanical strain, but represents activity of the essential rheumatic process in the heart. The course in our fatal cases, supported by postmortem study as well as parallel observations on our group of living patients, is in agreement with this conception. Although in cases of otherwise obscure involvement careful search usually reveals evidence of rheumatic activity, occasionally heart failure remains the only demonstrable evidence. The presence of nodules, otherwise often overlooked, has been particularly

3. Jones, T. D., and Bland, E. F.: Clinical Significance of Chorea as a Manifestation of Rheumatic Fever, J. A. M. A. **105**:571 (Aug. 24) 1935.

4. Rothschild, M. A.; Kugel, M. A., and Gross, L.: Incidence and Significance of Active Infection in Cases of Rheumatic Cardiovascular Disease During the Various Age Periods, Am. Heart J. **9**:586 (June) 1934.

helpful in disclosing clinically the relation between active rheumatic fever and heart failure—a relation to which postmortem study in this series has as yet revealed no exceptions. Therefore, in 21 instances in which the clinical notes were otherwise inadequate we have considered the presence of congestive failure as evidence per se of active rheumatic fever.

Acute fibrinous pericarditis, recognized clinically by a pericardial friction rub, was noted during the final illness in 35 per cent of the 135 patients who died of rheumatic fever at the House of the Good Samaritan. Of those studied post mortem, 55 per cent showed evidence of acute pericardial inflammation, whereas 80 per cent showed evidence of either acute or chronic pericardial involvement. Excessive amounts of pericardial fluid, beyond 200 cc., were rarely encountered. In 1 instance 800 cc. was removed by paracentesis, and in a second instance 1,200 cc. was removed post mortem. In the latter instance pericardial paracentesis in the fifth left interspace just inside the left border of cardiac dulness had yielded arterial blood (left ventricle) and no fluid. It is of further interest that in spite of the high incidence of pericardial involvement with rheumatic fever no instance of Pick's syndrome has yet been encountered.

Electrocardiograms taken at frequent intervals for the patients who have died in the House of the Good Samaritan since 1928 proved to be of no value in predicting the fatal outcome. In 40 per cent there was a delay in the auriculoventricular conduction time beyond the accepted normal of one-fifth second. In only 2 instances was the delay of sufficient extent to cause "dropped beats." It happened that these 2 patients were receiving moderate amounts of digitalis, which may have been in part responsible for the higher degree of block. No instance of complete auriculoventricular dissociation or of an intraventricular conduction defect was encountered. An abrupt and striking slowing of the pulse rate from a level of from 110 to 130 to a level of from 60 to 70 per minute occurred for a few hours before death in 6 patients. In 1 instance an electrocardiogram was obtained during this phenomenon and showed sinus bradycardia but no defect in conduction. The explanation for this occasionally observed terminal slowing of the pulse remains obscure.

Auricular fibrillation was present in 18 per cent of the patients, in spite of the youthfulness of the majority of them. The youngest patient in whom we have seen this arrhythmia was 7 years old, this disorder being the terminal event for two days prior to death. It may have been significant that this patient was receiving full doses of digitalis at the time. The youngest patient with established fibrillation was 9 years of age, and the arrhythmia persisted until death occurred two years later. In 4 additional cases auricular fibrillation ensued at the age of 11 years.

It is of considerable significance that in 36 (80 per cent) of a total of 45 patients who had auricular fibrillation a recrudescence of rheumatic fever was clearly the precipitating event. Paroxysmal tachycardia (presumably of auricular origin) occurred in 5 patients during severe rheumatic fever. Death occurred abruptly during the course of severe infection in 17 of the children who died at the House of the Good Samaritan. It suggests as a terminal event the occasional occurrence of either ventricular fibrillation or standstill of the heart.

2. *Pulmonary Signs.*—Evidence of involvement of the lung other than the simple congestion of heart failure or an associated pleural effusion was observed in 28 per cent of the patients under observation in the hospital during their final illness. Areas of consolidation, variable in size and distribution but usually bilateral, were encountered during severe exacerbations, especially in the cases of fulminant involvement. An associated pleural friction rub was common with underlying consolidation; less often a friction rub alone constituted the only clinical sign of pulmonary and pleural involvement. Post mortem these areas of consolidation represented gross hemorrhage in the pulmonary tissue, which has been discussed by others and designated rheumatic pneumonia. The physical signs associated with these lesions in a number of instances prior to study in the hospital were incorrectly attributed to primary disease of the lungs (pneumonia). It is to be emphasized that in our experience we have not encountered this consolidation as an isolated phenomenon but only as a complication in patients otherwise ill with a severe type of rheumatic fever.

3. *Hepatic Signs.*—In the present series striking changes were constantly observed in the liver both clinically and pathologically. In previous reports the hepatic signs have received relatively little attention. Enlargement (and tenderness) of the liver, both in the absence of and out of proportion to general venous engorgement, has been an outstanding features in the fatal cases. Postmortem observation not only confirms the constancy of this finding but reveals characteristic changes. Grossly the appearance is that of an enlarged congested liver presenting on section an unusually mottled "nutmeg" appearance. In cases of extreme involvement extensive areas of hemorrhage are present and occasionally deposits of fibrin superficially. Microscopic examination reveals widespread destruction of hepatic cells in the central portion of the lobules out of proportion to and apparently independent of the degree of associated congestion. The pattern in cases of severe involvement resembles that observed in certain types of severe toxemia. In spite of the extensive damage, clinical jaundice was rarely encountered (4 instances). So impressed have we been by the alterations observed post mortem that a detailed investigation of their significance is now in progress.

OTHER CONSIDERATIONS

From the total group of 306 patients who have died there remain 56 (18 per cent) in whom factors other than rheumatic fever were primarily responsible for the fatal termination.

Secondary bacterial infection of cardiac valves previously scarred by rheumatic fever accounted for 18 deaths (6 per cent). In 4 of these 18 patients acute bacterial endocarditis was responsible for death. The youngest patient was 3 years of age, and a pneumococcus was the causative organism. In the remaining 14 cases the clinical course was that of subacute bacterial endocarditis. Streptococcus viridans was the responsible agent in each instance. The youngest patient who died of subacute bacterial endocarditis was 6 years of age, death occurring three years after the onset of rheumatic fever. It seems to us that 6 per cent is a discouragingly high figure in view of the fact that we are dealing here with a group of young patients during the first decade after rheumatic fever and an age group in which bacterial endocarditis (especially the subacute type) is generally considered an infrequent complication.

There remain a few additional instances in which the cause of death was apparently related to the heart. Sudden death occurred in 6 patients with known rheumatic heart disease. We have observed sudden death in older apparently well patients in whom postmortem study revealed active rheumatic myocarditis as the only reasonable explanation.[5] It happened that autopsies were not performed on this group of 6 patients. In 3 of the remaining patients cerebral embolism, unassociated with known rheumatic activity or with bacterial endocarditis, resulted in death. In the remaining 29 patients the cause of death was either clearly unrelated to the heart or, as in 13 instances, entirely unknown.

SUMMARY AND CONCLUSIONS

Since 1921 (sixteen years) approximately 1,500 children and adolescents under the age of 21 years have received hospital care at the House of the Good Samaritan for rheumatic fever and chorea. The subsequent course and present status of this large group are known. We have presented in this report data relevant to the 306 patients who have died. Postmortem examination was made in 74 instances (24 per cent). From a consideration of this group of patients who have died the following conclusions may be cited:

1. Rheumatic fever has been the outstanding cause of death and was directly responsible for the fatal issue in 250 instances (82 per cent).

5. Rheumatic Myocarditis, Cabot Case 22041, New England J. Med. **214**:154 (Jan. 23) 1936.

2. The early years after the onset of the disease have proved to be a critical period. In approximately half (47 per cent) of the fatal cases death occurred during the first three years and in two-thirds (62 per cent) during the initial five years.

3. Thereafter the extent of residual cardiac enlargement (dilatation) and, to a lesser degree, the rapidity with which it developed have served as the most reliable criteria of the severity of the preceding infection as well as an index of the future susceptibility of the individual patient to subsequent fatal rheumatic fever.

4. The age of the patient at the time of onset of rheumatic fever (or chorea) during the first fifteen years of life has been of no significance so far as subsequent longevity is concerned.

5. The manifestations of fatal rheumatic fever have been stressed and contrasted with the generally accepted clinical picture of the disease.

ATYPICAL FACIAL NEURALGIA

AN ANALYSIS OF TWO HUNDRED CASES

MARK ALBERT GLASER, M.D.
AND
H. MARLIN BEERMAN, M.D.
LOS ANGELES

The occurrence of continuous and obscure pains about the face and head for which the usual methods of relief, both medical and surgical, have as a rule failed has been the subject of considerable investigation since 1920. The patients whose records are here analyzed have run the gantlet of numerous physicians, both local and foreign, 1 patient (who is a physician) having visited 126 physicians in America and on the Continent. Useless and meddlesome surgical procedures have been performed not only on the trigeminal tract but on the nasal sinuses, the abdomen and the pelvis, and there has been wholesale extraction of teeth as well. Peculiarly enough, not only have these operations failed to accomplish their purpose, but in practically all cases the pain has been much worse thereafter.

Though many of these patients complain bitterly of pain during the examination, their facies rarely indicate such severity. This is in contradistinction to patients with trigeminal neuralgia, who during an attack show every indication of the excruciating nature of the pain.

From 1908 to 1916 Sluder [1] observed that the bony partition separating the accessory nasal sinuses from the sphenomaxillary fossa may be extremely thin or even defective. He said he believed that inflammation within these cells may cause involvement of the sphenopalatine ganglion, with the resulting development of a neuralgic syndrome, which he described as follows:

> The neuralgic picture is pain in the root of the nose and in and about the eye, in the upper jaw and teeth (sometimes lower jaw and teeth) extending backward under the zygoma to the ear, frequently making earache and pain in the mastoid; but severest often at a point 6 cm. back of the mastoid, extending thence to the occiput, neck, shoulder-blade, shoulder, breast, and when severe, to the arm, forearm, hand and fingers; with sometimes a sense of sore throat on that side. Rarer additions to this picture are itching of the skin of the upper extremity, taste disturbances (parageusia), a sense of stiffness and muscle weakness in the upper extremity and fortification scotomata. Mild cases are described as a sense

1. Sluder, G.: Headaches and Eye Disorders of Nasal Origin, St. Louis, C. V. Mosby Company, 1918.

of tension in the face and stiffness or rheumatism in the shoulders. It may appear as a constant pain with exacerbations, or it may stop and reappear cyclically as a migraine; or it may stop and reappear with stabbing sharpness as a tic.

In 1920 Cushing [2] reported the case of a woman 35 years of age, who first came under his observation in 1906 because of facial pain. After numerous injections of alcohol, peripheral neurectomy and evulsion of the trigeminal root, she still complained of pain in spite of the existence of anesthesia. A diagnosis of sphenopalatine neuralgia was made, and twice injection of alcohol into the sphenopalatine ganglion was attempted without affording relief. Finally the sphenopalatine ganglion was surgically removed, still without relief. In January 1920, thirteen years later, the patient still had the original pain. Cushing has observed 6 or 8 similar cases, and this experience has led him to beware of patients with this type of pain.

In 1923 Davis [3] reported on a patient with continuous pain in the face, right enophthalmos, with drooping of the upper eyelid, a slightly smaller pupil on the right and increased lacrimation on the right. This patient was not relieved by injections of alcohol or of cocaine into the sphenopalatine ganglion.

In 1923 Frazier and Russell [4] called attention to the existence of a miscellaneous group of these neuralgias to which, for want of better understanding as regards origin and treatment and for want of better terminology, the name atypical neuralgia was applied. After analyzing 60 cases they enumerated some diagnostic points which enable one to differentiate these neuralgias from true trigeminal neuralgia, thus avoiding section of the sensory root. At that time they emphasized the constant character of the pain, stating definitely that it was not intermittent but paroxysmal, though varying in its intensity.

Reid and Eckstein,[5] in 1924, called attention to cases of neuralgia of the face in which relief was not obtained by excision of the trigeminal nerve. They quoted Heuer, who had the opportunity of examining a patient who had been operated on eight years before and was not completely relieved by division of the sensory root of the fifth nerve. They found that pressure on the superior cervical ganglion produced

2. Cushing, Harvey: The Varieties of Facial Neuralgia, Am. J. M. Sc. **160**:157 (Aug.) 1920.

3. Davis, Loyal E.: Lesions of the Paratrigeminal Area, J. A. M. A. **80**:380 (Feb. 10) 1923.

4. Frazier, C. H., and Russell, Ethel C.: Neuralgia of the Face: An Analysis of Seven Hundred and Fifty-Four Cases with Relation to Pain and Other Sensory Phenomena Before and After Operation, Arch. Neurol. & Psychiat. **11**:557 (May) 1924.

5. Reid, Mont R., and Eckstein, Gustav: Sensory Disturbances Following Sympathectomy for Angina Pectoris, J. A. M. A. **83**:114 (July 12) 1924.

pain in all three branches of the fifth nerve, though the face was totally anesthetic. Three years later Fay [6] again called attention to the sign and applied the word carotidynia.

Parker,[7] in 1924, described several cases of unusual facial pain in the area of the fifth nerve, resulting from various etiologic factors. He further deplored the use of the word atypical, which was in line with the opinion of Frazier and Russell.

In 1928 Glaser [8] reviewed the cases from Frazier's clinic and found 245 examples of the atypical variety. From the 245 he segregated 143 with similarity of symptoms, namely, the lack of response to therapy and the absence of any etiologic factor. Because of inability to supply a better name than that first suggested by Frazier, this particular group was defined as representing atypical neuralgia. From this study a clear-cut syndrome was drawn up. No method of treatment was suggested, as all attempts directed toward relief had failed, and attention was called to the importance of the recognition of these cases.

In this original analysis of 143 cases, constancy of pain also was dominant. In none of the cases was there evidence of short attacks of pain lasting for from several hours to several days. In cases in which an intermission of several years occurred an oppressive sensation persisted. None of these attacks could be considered intermittent or paroxysmal. Those of this nature were entirely eliminated from the analysis and belonged among the remaining 102 cases eliminated from this series.

Reports concerned with patients suffering from obscure facial pains have appeared in the literature from time to time (Foerster;[9] Halphen, Monbrun and Tournay;[10] Peet;[11] Grant;[12] Flothow;[13] White;[14]

6. Fay, Temple: Atypical Neuralgia, Arch. Neurol. & Psychiat. **18**:309 (Aug.) 1927; Atypical Facial Neuralgia, A Syndrome of Vascular Pain, Ann. Otol., Rhin. & Laryng. **41**:1030 (Dec.) 1932.

7. Parker, Harry L.: Unusual Forms of Pain in the Area of the Fifth Nerve, J. A. M. A. **83**:1672 (Nov. 22) 1924.

8. Glaser, Mark A.: Atypical Neuralgia, So-Called: A Critical Analysis of One Hundred and Forty-Three Cases, Arch. Neurol. & Psychiat. **20**:537 (Sept.) 1928.

9. Foerster, O.: Deutsche Ztschr. f. Nervenh. **106**:109 (Dec.) 1928.

10. Halphen, Monbrun and Tournay: Les céphalées en oto-neuro-ophtalmologie; Physiologie pathologique et traitement, Rev. d'oto-neuro-opht. **7**:161 (March) 1929.

11. Peet, Max Minor: The Rôle of the Sympathetic Nervous System in Painful Diseases of the Face, Arch. Neurol. & Psychiat. **22**:313 (Aug.) 1929.

12. Grant, Francis: Personal communication to the authors, Jan. 20, 1930.

13. Flothow, P. G.: Relief of Pain from a Neurological Viewpoint, Northwest Med. **29**:69 (Feb.) 1930.

14. White, James C.: Progress in the Surgery of the Sympathetic Nervous System in 1932, New England J. Med. **209**:843 (Oct. 26) 1933.

Mixter and White;[15] Reichert;[16] Davis and Pollock;[17] Abbott;[18] Wilson;[19] Fincher;[20] Turner;[21] Braeucker;[22] Marks;[23] Bryan;[24] Hyslop;[25] Brickner and Riley;[26] Merwarth,[27] and Cobb and Mixter[28]).

The present paper deals with 200 cases in which there was constant pain (143 of these cases have been previously reported) and which have been analyzed in order to show some of the characteristics. A further classification of obscure facial pains, as well as the etiology and treatment in some cases, will be the subject of another communication.

Numerous operations have been performed for the relief of atypical facial neuralgia, but none of them has been successful in this particular group. In approximately half the cases included in table 1 the patient was unable to relate the onset of pain to any particular cause, though in table 2 there may be noted numerous coincidental events from which the patient thought the pain might have originated. According to table 3 the onset was most common in the third decade of life, and in the majority of cases the pain developed in early life. Females greatly predominated over males, as shown in table 4, while table 5 shows that the pain occurred on the right, on the left and bilaterally almost equally. The distribution of the pain followed, in general, a circular area within the facial vascular supply. The pain was felt in the chin, along the nose, around the eye, over the brow, to the vertex or temporal region, in front of, in or

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26. Brickner, Richard M., and Riley, Henry Alsop: Autonomic Facio-Cephalalgia, Bull. Neurol. Inst. New York **4**:422 (Dec.) 1935.

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TABLE 1.—*Number of Operations of Various Types*

Injection of alcohol in branches of trigeminal nerve	70
Injection of cocaine into sphenopalatine ganglion	66
Extraction of teeth	74
Operation on sinuses	60
Avulsion of supra-orbital and infra-orbital nerves	24
Nasal operation	21
Cervical sympathectomy	12
Stripping of periarterial carotid plexus	10
Subtotal section of sensory root of trigeminal nerve	12
Mastoidectomy	8
Pelvic operation	8
Paravertebral block	3
Appendectomy	2
Tonsillectomy	2
Operation on brain	1
Removal of lipoma of left eye	1
Excision of artery	1

TABLE 2.—*Coincidental Events*

Extraction of teeth	38
Accidents	
War wounds	4
Automobile accident	9
Railroad accident	2
Blow on head	1
Diseases	
Influenza	7
Cold	4
Gastro-intestinal disorder	2
Operation	13
Worries	9
Pregnancy	1
Nervous breakdown	3
Facial tic	1
Cocaine addiction	1
Unknown	105

TABLE 3.—*Age at Onset*

Age	Number of Cases
0-10	19
10-20	39
20-30	56
30-40	38
40-50	22
50-60	11
Unknown	15

TABLE 4.—*Incidence According to Sex*

Sex	Number of Cases
Male	48
Female	152

TABLE 5.—*Side Involved*

	Number of Cases
Left	66
Right	58
Both	76

through the ear and thence down into the suboccipital region. Occasionally it entered the shoulder, rarely the body. This wide area of distribution could occur in a single case (figure) or individual areas, or various combinations of areas could exist (table 6).

The character of the pain is extremely difficult to describe, numerous adjectives being utilized by the patients. In all, some seventy different adjectives and terms were utilized. This pain was never superficial;

TABLE 6.—*Distribution of Pain Through Course of Disease*

		No. of Cases
A	Individual areas	24
	1. Lower jaw, upper jaw, inside of mouth	13
	2. Eye, supra-orbital region	8
	3. Cheek, suboccipital region	3
B	Lower jaw to {Upper jaw / Malar region / Nose} {Over eye / In eye / Under eye} {Frontal area / Temporal area / Parietal area} {Behind ear / Through ear / Front of ear} {Occipital region / Suboccipital region / Neck / Shoulder / Arm}	28
B_1	{Upper jaw / Malar region / Nose} To complete arc as in B	47
B_2	{Over eye / In eye / Under eye} To complete arc as in B	33
B_3	{Frontal area / Temporal area / Parietal area} To complete arc as in B	9
C	Lower jaw to {Upper jaw {Malar region / Nose}} Eye {Ear {Temporal area {Neck	20
C_1	Upper jaw to {Malar region / Nose} Eye {Ear {Temporal area {Neck	23
C_2	Eye to {Ear {Temporal area / Frontal area}	9
C_3	{Temporal area / Frontal area / Parietal area}	6
D	Body paresthesias plus B	1
	Total	200

it was always deep seated and aching, burning or throbbing. In addition to those enumerated in table 7, the following descriptions were used: The sensation was like tearing celery, a thousand fishhooks pulling and tugging on the face, birds flying under the skin, the pounding of a hammer on the face, a hot poker back of the eye, the cutting away of pieces of bone or muscle beneath the skin, a bruise, a saw cutting the face, something in the jaw, a mass of fire, pins and needles, stiffness, the feeling of menthol, the buzzing of a mosquito, a log on top of the head, a full feeling, a hard knot deep in the eye, the bursting of an eyeball, the pushing of the eye through the head, drawing out the eye

or a ball of fire or electricity in the eye. Some patients described it as twitching, severe, jumpy, crawling, unbearable, wearing, pounding, surging, crushing, vibrating, excruciating or grabbing.

The pain was chronic, persistent and continuous, and associated with it were attacks of greater or less severity, which would come on either acutely or insidiously. If an attack of pain had an insidious onset, it would gradually increase in intensity over a period of from several hours to several days. Then the pain would be at its height over a period of from several hours to several days. During the period of most severe pain associated sympathetic phenomena were present in some cases and the patient would necessarily be confined to bed. The attack might then

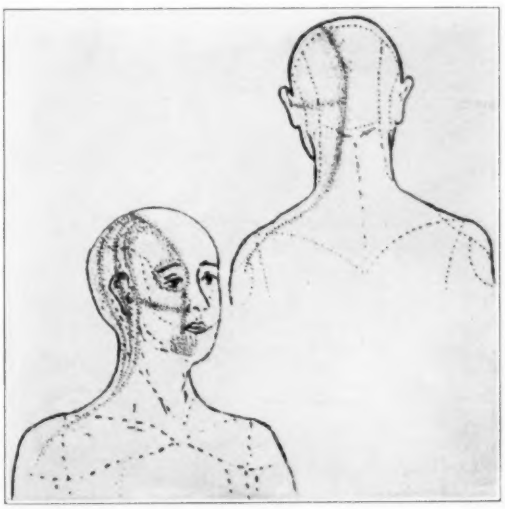
TABLE 7.—*Type of Pain*

	Number of Cases
Dull aching	88
Throbbing	58
Burning	53
Shooting	50
Sharp	42
Sense of pressure	39
Drawing	30
Needle-like	26
Boring	24
Toothache	22
Pulling	21
Soreness	18
Gnawing	17
Bursting	14
Tearing	14
Electricity	14
Hot iron	12
Tingling	11
Smarting	11
Nagging	11
Knifelike	9
Beating	9
Stinging	9
Pricking	8
Bugs creeping	8
Itching	8
Gripping	7
Lightning	4

either suddenly subside or gradually disappear. After that there was the chronic phase of the disease. These attacks might occur at intervals of several days to even months, but during the interim between attacks the patient was never free from pain. If a remission did occur, as it did in a few cases, the picture of the neuralgia did not give the impression of being paroxysmal or intermittent. It is the constancy of the pain that makes up this syndrome. In no case in this particular group was relief obtained by any therapeutic measure, though table 8 indicates some of the methods whereby a certain amount of ease was found. The local factors that aggravated the pain consisted of eating, contact, brushing the teeth, blowing the nose, sneezing, swallowing and shaving and were present in 35 cases, whereas in the remaining 165 cases general factors were responsible for the onset. In all the cases in which local factors

were responsible for aggravating the pain, general factors also brought on the attack. Sympathetic phenomena were present in 90 cases, whereas in the remaining 110 cases there was no sympathetic involvement.

This pain must be mainly differentiated from that of trigeminal neuralgia. The incidence of tic douloureux is equal in the two sexes, whereas in the cases of atypical neuralgia females predominate. Tic douloureux is bilateral in only 2 per cent, whereas atypical neuralgia is bilateral in one third of the cases. Tic douloureux usually occurs in persons over 35 years of age, whereas atypical neuralgia occurs more frequently in younger persons. Tic douloureux always follows the



The distribution of the pain in atypical facial neuralgia.

distribution of the trigeminal nerve, whereas atypical neuralgia follows the distribution of no single cranial nerve. The pain in tic douloureux is superficial, whereas that of atypical neuralgia is deep. When the trigeminal nerve is affected, there are intervals of freedom from pain, whereas in cases of atypical neuralgia pain of some type is always present. Both of these diseases may be marked by attacks of pain; but the attack of trigeminal neuralgia is short and terrifically painful, while the attack of atypical neuralgia is long, with pain of less intensity. The type of pain in trigeminal neuralgia is lancinating, sharp and knifelike, whereas that of atypical neuralgia is aching, burning and nagging, being extremely difficult to describe. The pain of trigeminal neuralgia is brought on by the slightest local contact, while that of atypical neuralgia

is brought on by more generalized factors, such as cold, fatigue or excitement. Trigger zones occur in trigeminal neuralgia, while tenderness of the cervical sympathetic ganglion or the cervical artery is present

TABLE 8.—*Factors Which Eased the Pain*

	Number of Cases
Acetylsalicylic acid	31
Heat	24
Morphine	23
Nothing	18
Pressure	13
Lying down	11
Cold	9
Codeine	8
Massage	6
Dark room	4
Smoking	3
Chewing (paraffin in 2 cases)	3
Epinephrine hydrochloride (spray)	2
Hot weather	2
Pressure on jugular vein	2
Nonuse of eyes	1
Chloral hydrate	1

TABLE 9.—*Factors Aggravating the Pain*

	Number of Cases
Local	
Cold	68
Draft	34
Heat	32
Eating	22
Light	14
Contact	15
Brushing teeth	12
Vibrating	11
Reading	15
Wind	8
Blowing nose	8
Sneezing	8
Swallowing	6
Shaving	2
General	
Fatigue	63
Excitement	48
Menses	36
Worry	34
Talking	27
Winter	15
Exertion	17
Night	16
Lying down	17
Stooping	13
Morning	11
Noise	18
Damp	13
Motion	3
Cough	7
Arguments	1
Washing face	1
Constipation	1
Nothing	14

in atypical neuralgia. Tic douloureux is entirely without associated sympathetic phenomena, but in approximately 50 per cent of the cases of atypical neuralgia there are sympathetic phenomena.

As there are other cranial nerves which have a sensory supply to the face, it may occasionally be found that a disorder of these nerves is confused with atypical facial neuralgia. These neuralgias are paroxysmal, with acute lancinating pain referred to the distribution of the nerve involved. Foremost among this group is glossopharyngeal neuralgia,

TABLE 10.—*Sympathetic Phenomena*

	Number of Cases
Ocular disturbance	
Lacrimation	52
Edema	46
Corneal injection	26
Unequal pupils	20
Blurred vision	6
Photophobia	4
Enophthalmos	2
Nausea	39
Vomiting	34
Flushing of face	28
Nasal discharge	21
Perspiration	14
Salivation	11
Puffy face	13
Feeling of warmth	2
Ringing in ears	2
Soreness over temporal artery	1
Chills	2
Aural discharge	3

TABLE 11.—*Differentiation of Tic Douloureux and Atypical Neuralgia*

	Tic Douloureux	Atypical Neuralgia
Sex incidence	Equal	Predominance of females
Bilateral pain	In 2% (approximate)	In 33% (approximate)
Age	35 years and over	35 years and under
Distribution	Trigeminal nerve	No single cranial nerve
Attacks	Momentary; very severe	Long; less severe
Pain	Intervals of freedom	Continuous
	Superficial	Deep
	Lancinating; sharp; knifelike	Aching; boring; throbbing; extremely difficult to describe
Onset following	Slightest stimulation of skin or mucous membrane	Cold; fatigue; excitement
Trigger zones	Trigger zones along trigeminal nerve (frequently)	Tenderness on pressure in area of carotid and cervical sympathetic ganglions (frequently)
Sympathetic phenomena	None	In 50%
Narcotic addiction	None	Frequent

in which the pain is paroxysmal, sharp, shooting and lancinating, usually beginning in the throat or tonsillary region or back of the tongue, then radiating in front of the ear, down the throat, into the jaw and occasionally into the neck. Occasionally these patients complain of a "hacking" cough, sometimes the tic seems to be relieved by pain in the ear and occasionally a feeling of dryness of the mouth and salivation accompanies the syndrome. A trigger zone at times may be found at the

base of the tongue or tonsillar region, and an injection of cocaine will temporarily relieve the attack. These attacks are always brought on by an effort on the part of the patient, such as talking, eating or swallowing. Surgical section of the glossopharyngeal nerve always relieves the pain (Weisenburg,[29] Harris,[30] Doyle,[31] Sicard and Robineau,[32] Reichert,[33] Adson,[34] Dandy [35] and Stookey [36]).

In 1927 Fay [37] expressed the opinion that the sensory fibers of pain distribution to the pharynx and to the region of the ear, in the zone of so-called glossopharyngeal neuralgia, do not correspond to a function of the ninth nerve and its intracranial representation. He said he considered this syndrome as a manifestation of the tenth nerve in the sensory portion and suggested the name vagal auricular pharyngeal neuralgia. No work has been carried out to corroborate Fay's opinion; and in view of the numerous cases of glossopharyngeal neuralgia in which relief has followed section of the ninth nerve, this idea has not gained recognition.

Neuralgia of the superior laryngeal nerve has been described by Avellis,[38] Hutter,[39] Bailey,[40] Harris [30] and Echols and Maxwell.[41] It is

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32. Sicard, R., and Robineau: Algie vélopharyngée essentielle; traitement chirurgical, Rev. neurol. **27**:256, 1920.

33. Reichert, Frederick Leet: Glossopharyngeal Neuralgia, West. J. Surg. **39**:347 (May) 1931.

34. Adson, A. W.: The Surgical Treatment of Glossopharyngeal Neuralgia, Arch. Neurol. & Psychiat. **12**:497 (Nov.) 1924.

35. Dandy, W. E.: Glossopharyngeal Neuralgia (Tic Douloureux): Its Diagnosis and Treatment, Arch. Surg. **15**:198 (Aug.) 1927.

36. Stookey, B.: Glossopharyngeal Neuralgia: Surgical Treatment, with Remarks on the Distribution of the Glossopharyngeal Nerve, Arch. Neurol. & Psychiat. **20**:702 (Oct.) 1928.

37. Fay, Temple: Intracranial Division of Glossopharyngeal Nerve Combined with Cervical Rhizotomy for Pain in Inoperable Carcinoma of the Throat, Ann. Surg. **84**:456, 1926.

38. Avellis, G.: Typische Form von Kehlkopfneuralgie, München. med. Wchnschr. **47**:1592 (Nov. 13) 1900.

39. Hutter, F.: Ueber Neuralgien des Nervus laryngeus superior, Monatschr. f. Ohrenh. **63**:402 (April) 1929.

40. Bailey, Percival: Neuralgias of Cranial Nerves, S. Clin. North America **11**:61 (Feb.) 1931.

41. Echols, Dean H., and Maxwell, James H.: Superior Laryngeal Neuralgia Relieved by Operation, J. A. M. A. **103**:2027 (Dec. 29) 1934.

characterized by paroxysms of unilateral pain, which radiates from the side of the thyroid cartilage to the angle of the jaw and occasionally to the ear. There is a trigger zone at the plica of the nerve in the pyriform sinus. Swallowing will bring on an attack. There is a sensitive point superficially situated, above and lateral to the thyroid cartilage, where the nerve pierces the hypothyroid membrane.

The sensory innervation of the auricle and surrounding skin is complex. The trigeminal, the facial, the vagus and pneumogastric (it is almost impossible anatomically to separate the pneumogastric sharply from the vagus nerve), the glossopharyngeal and the greater auricular nerve, which arises from the second and third cervical nerves, supply this area. As these areas overlap considerably, it is extremely difficult to determine the exact nerve responsible for pain. There is a group of neuralgias of the acute lancinating variety which has been variously described in the literature under different names. Hunt [42] said he believed that the pain is due to involvement of the facial nerve. Taylor and Clark [43] operated on a patient and demonstrated that the pain was in the pars intermedia of Wrisberg. Reichert [44] operated on another patient, demonstrating the glossopharyngeal nerve as the responsible factor. Hall [45] stated that he was under the impression that the greater auricular nerve caused the pain in his particular patient. Suffice it to say that acute neuralgia is extremely rare but must be considered in conjunction with vidian and sphenopalatine neuralgias in their differentiation from the more chronic type of so-called atypical neuralgia.

CONCLUSIONS

The term atypical neuralgia is not satisfactory but has been used by Frazier, Russell and Glaser to describe a peculiar deep-seated, aching pain that is constant, not paroxysmal or intermittent, but marked by attacks of greater or less severity, occurring at varying intervals. Remissions are rare. Associated with this pain are sympathetic phenomena in 50 per cent of the cases. The pain does not follow the distribution of any of the cranial nerves and involves the scalp as well as the face.

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EFFECT OF EXPERIMENTAL CARDIAC INFARCTION ON RESPONSE TO DIGITALIS

JANET TRAVELL, M.D.

HARRY GOLD, M.D.
AND
WALTER MODELL, M.D.
NEW YORK

In 1925 a study was published by one of us (Dr. Gold[1]) on the tolerance of the cat to ouabain in the presence of coronary occlusion. It was found that within periods up to twenty-four hours after extensive ligation of coronary vessels animals required on the average as much ouabain to cause death as did normal animals. These results were confirmed in a recent study (1934) by Bellet, Johnston and Schecter,[2] in which the drug was digitalis, the interval between the ligation and the testing was thirty minutes and the animal used was the dog. These authors extended their study to include chronic experiments, and from them they found that four days after the ligation the tolerance to digitalis had diminished by about 23 per cent of normal but that in from six weeks to six months some recovery of tolerance had taken place (tolerance being reduced about 14 per cent). The latter figure, however, represents an average of results for only four animals with two specimens of digitalis. Two other observations aroused our interest: first, that the reduction in tolerance appeared to be proportional to the size of the infarct and, second, that the cat appeared to behave differently from the dog, for in preliminary experiments it was observed that in the cat no diminution of tolerance to digitalis occurred from six to eleven days after ligation of a coronary vessel.

Both of these observations were significant and appeared to be in need of stronger support. An opportunity presented itself to look into this matter in the course of another investigation,[3] in which a large number of cats had survived for three weeks after acute cardiac infarction. The effect of digitalis under these conditions was investigated, and the results form the subject of the present report.

From the Department of Pharmacology, Cornell University Medical College.

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2. Bellet, S.; Johnston, C. G., and Schecter, A.: Effect of Cardiac Infarction on the Tolerance of Dogs to Digitalis, Arch. Int. Med. **54**:509 (Oct.) 1934.

3. Gold, H.; Travell, J., and Modell, W.: The Effect of Theophylline with Ethylenediamine (Aminophylline) on the Course of Cardiac Infarction Following Experimental Coronary Occlusion, Am. Heart J. **14**:284 (Sept.) 1937.

EXPERIMENTAL METHOD

Experiments were carried out on fifty cats. The same tincture of digitalis was used in all the experiments.

The method of testing tolerance was uniform. All operations were performed with the animal under local anesthesia. The tincture was diluted twenty times with physiologic solution of sodium chloride and injected into the saphenous vein from a buret until there was cessation of the heart beat, which was always preceded by a convulsion. The solution was adminstered by the interrupted method, a dose equivalent to approximately 2.5 per cent of the cat unit being injected at intervals of two minutes.

An electrocardiogram (lead II) was taken just before the injection of each 2.5 per cent fraction.

The blood pressure throughout the experiment was recorded from the carotid artery by a mercury manometer. Clotting was prevented by the occasional injection of about 0.2 cc. of a 5 per cent solution of chlorazol pink into the system near the cannula.

The animals with cardiac infarcts were those included in another investigation, and the details of the technics, as well as the condition of the animals, were described in that report.[3] Briefly, the coronary vessel that was ligated was the left circumflex artery, except in two instances: The left descending artery was ligated in one and the left circumflex branch together with the right coronary artery in the other. Detailed autopsies were made in all cases. The area of the infarct was measured with a planimeter after reproduction of the outlines on glass or paper.[3]

RESULTS

The effects of digitalis were compared for three groups of cats:

Group A. Animals three weeks after ligation of the coronary artery (table 1)

Group B. Animals three weeks after a control operation, in which the coronary vessel was exposed but not ligated (table 2)

Group C. Animals on which no operation was performed.

Influence of Infarction on Various Actions of Digitalis.—A. Fatal Dose: The average fatal dose of the tincture, determined by the technic of injection employed in this study, was 0.82 (0.51 to 1.05) cc.[4] per kilogram for the normal animal (nine cats). The average body weight for this group was 2.65 Kg., and the average period of injection was seventy-one minutes.

In groups A and B, both comprising animals that had been operated on and had been kept under special conditions for three weeks, it was necessary to take account of the change in body weight in calculating the fatal dose. The tolerance of an animal to digitalis changes with a loss of weight, but it has been found [5] that the fatal dose per kilogram after starvation is the same as that for the normal animal when the total dose

4. It is interesting to note that a slight modification of the technic did not appreciably change the size of the fatal dose, for an essentially similar result was obtained (0.85 cc.) as the cat unit of this specimen in an assay carried out on eight cats a few months previously, the injection in that case having been continuous and the average duration of the injection having been sixty minutes.

5. Gold, H.: Digitalis Elimination, Arch. Int. Med. **32**:779 (Nov.) 1923.

TABLE 1.—*Results for Twenty-Nine Animals Three Weeks After Ligation of Coronary Artery*

Cat No.	Fatal Dose of Tincture of Digitalis, Cc. per Kg.	Size of Infarct, Sq. Cm.	Mean Blood Pressure Before Digitalis, Mm. Hg	Change in Weight, Percentage	Dose Causing Ventricular Ectopic Rhythm, Cc. per Kg.
1	1.13	2.65	183	+ 3.4	0.19
2*	0.92	3.68	170	+ 2.3	0.56
3	0.78	5.94	175	— 6.0	0.36
4	0.76	6.39	133	—21.2	0.45
5*	0.73	2.90	120	—14.8	0.35
6*	0.71	3.23	150	—13.3	....
7	0.70	4.19	170	+ 7.2	0.36
8	0.66	4.45	159	+ 1.4	0.18
9	0.65	3.74	155	—13.8	0.50
10*	0.63	5.94	153	—13.2	0.43
11*	0.62	6.97	150	+ 7.3	0.24†
12	0.62	5.61	135	—14.2	0.47
13*	0.61	3.23	146	—19.4	0.33
14*	0.59	3.55	146	—14.1	0.42
15*	0.56	5.74	135	—24.5	0.49
16*	0.55	6.90	160	— 6.7	0.30
17	0.54	9.48	154	—13.5	0.29
18	0.53	3.94	133	—16.4	0.42
19*	0.53	6.97	133	—21.1	0.30
20*	0.52	9.81	148	—11.8	....‡
21	0.48	3.36	158	—16.3	0.28
22*	0.47	12.84	125	— 0.9	0.38
23*	0.46	5.29	144	—22.0	0.22
24	0.45	6.45	...	—10.8	0.36
25	0.44	2.58	155	— 6.9	0.37
26	0.43	6.07	161	—16.3	0.24
27	0.42	6.97	135	—15.8	0.29
28	0.37	7.36	155	—19.6	....
29	0.36	2.26	...	— 6.1	0.36
Averages	0.59	5.47	150	—10.9	0.35 (59.3% of M.L.D.)

* Treated with aminophylline.
† Ectopic beats were present in the electrocardiogram before the injection of digitalis.
‡ Idioventricular rhythm was present in the electrocardiogram before and throughout the injection of digitalis.

TABLE 2.—*Results for Twelve Animals Three Weeks After Control Operation*

Cat No.	Fatal Dose of Tincture of Digitalis, Cc. per Kg.	Mean Blood Pressure Before Digitalis, Mm. Hg	Change in Weight, Percentage	Dose Causing Ventricular Ectopic Rhythm, Cc. per Kg.
1	1.15	146	—11.2	0.51
2	0.91	160	— 6.7	0.63
3	0.88	143	— 6.1	0.56
4	0.86	120	—22.2	....
5	0.78	185	— 8.9	0.27*
6	0.73	147	—10.7	0.47
7	0.68	156	— 6.4	0.48
8	0.65	173	—17.2	0.38
9	0.63	152	—21.9	0.52
10	0.63	143	—30.7	0.23
11	0.62	181	—17.9	0.48
12	0.54	155	—16.4	0.41
Averages	0.76	155	—12.2	0.45 (59.2% of M.L.D.)

* Ectopic beats were present in the electrocardiogram before the injection of digitalis.

required is divided by the average of the original and the new body weight. This method of calculation was employed for the animals of groups A and B in order to exclude a change in body weight as a factor in any alteration in tolerance.

The average fatal dose for twelve animals three weeks after the control operation without ligation of the coronary vessel (group B) was 0.76 cc. per kilogram (table 2), or 7.4 per cent below that for the normal animals. This figure, however, is not significant, because it is

TABLE 3.—*Summary of Results After Control Operation and Ligation*

Operative Procedure	Average Body Weight, Kg.	Loss of Body Weight, Percentage	Mean Blood Pressure Before Digitalis, Mm. Hg	Period of Injection, Min.	Dose Causing Ventricular Ectopic Rhythm, Cc. per Kg.	Fatal Dose of Tincture of Digitalis, Cc. per Kg.	Tolerance to Fatal Action of Digitalis, Percentage of Normal
Control operation (12 cats).....	2.84	12.2	155	68	0.45	0.76	92.6
Ligation of coronary artery (29 cats).....	2.93	10.9	150	53	0.35	0.59	72.0

TABLE 4.—*Comparison of Results Three Weeks After Ligation of Coronary Artery for Animals Treated and Not Treated With Aminophylline*

	Averages for Groups	
	Not Treated (16 Cats)	Treated (13 Cats)
Average body weight, Kg.	2.96	2.89
Loss of body weight, percentage.....	10.3	11.7
Size of infaret, sq. cm.	5.10	5.94
Mean blood pressure before administration of digitalis, mm. Hg...	154	145
Period of injection of tincture of digitalis, min.	53	54
Dose at which ventricular ectopic rhythm appeared, cc. per Kg. ...	0.34* (58% M.L.D.)	0.36* (59% M.L.D.)
Fatal dose of tincture of digitalis, cc. per Kg.	0.58	0.61
Tolerance to fatal action of digitalis, percentage of normal.....	70.7	74.4

* The averages were based on the results for eleven animals which were treated and fifteen animals which were not treated with aminophylline.

within the range of variations which may exist in the results of a bioassay made by the use of two different groups of animals.

The average fatal dose for twenty-nine animals with infarction (group A) which were tested three weeks after ligation of the coronary artery was 0.59 cc. per kilogram (table 3), representing a reduction of tolerance by 28 per cent of that of the normal animal, or by 22 per cent of that of the group in which the control operation was performed.

The range of tolerance of the animals with cardiac infarction was from 39 per cent below (the most susceptible animal) to 91 per cent above (the most tolerant animal) the average. For the control animals the range was from 34 per cent below to 36 per cent above the average.

It may be seen (table 1) that thirteen of the twenty-nine animals with infarction had been treated with aminophylline in connection with another study.[5] Each of these had received a daily intramuscular injection, usually 25 mg. per kilogram, for twenty consecutive doses, the last dose being given about twenty-four hours prior to the injection of digitalis. The results for this group are treated separately in table 4, but since aminophylline appeared to exert no influence on the tolerance to digitalis, the two groups were combined and treated as one for the comparisons in this study. The observation that aminophylline does not influence the tolerance to the fatal action of digitalis is in harmony with the findings of Haag and Woodley.[6]

B. Ventricular Ectopic Rhythm: The electrocardiogram provided a means for determining the susceptibility to some of the other effects of digitalis. The T wave, the PR interval and the sinus rate were too variable under the conditions of these experiments to be used. The data were analyzed, however, (*a*) with respect to the dose required to produce a ventricular ectopic rhythm and (*b*) with respect to the influence of digitalis on the displacement of the RT segment.

In the control animals (group C) which were not operated on an average of 39 per cent of the fatal dose was required to produce a ventricular ectopic rhythm. This amount was smaller than that required to cause the same effect in another study, namely, 54 per cent of the fatal dose for seventy-seven cats.[7] It was also smaller than the figure which we obtained for the other two groups of animals (groups A and B), namely, 59 per cent for each group (tables 1 and 2). When an animal is excited and struggles, ectopic ventricular beats are likely to appear earlier in the course of digitalis poisoning than when the animal is quiet.[8] The animals that were not operated on struggled considerably, the period of assay being the first time that their freedom had been restricted.[9] This may account for the small dose which caused the ventricular ectopic rhythm to appear. The animals which were operated on without ligation of an artery provided a more valid control for the group with infarcts. The animals in both groups showed relatively little excitement during the injection of digitalis, having grown accus-

6. Haag, H. B., and Woodley, J. D.: The Effect of Caffeine and Theobromine on Digitalis Toxicity, J. Pharmacol. & Exper. Therap. **53**:465, 1935.

7. Gold, H.; Hitzig, W.; Gelfand, B., and Glassman, H.: A Qualitative Comparison of Various Digitalis Bodies, Am. Heart J. **6**:237, 1930.

8. Gold, H.; Lieberson, A., and Gelfand, B.: Mechanism of Production of Subauricular Beats by Digitalis Bodies, Arch. Int. Med. **48**:262 (Aug.) 1931.

9. In two of the nine animals not operated on ventricular ectopic beats were noted before the injection of digitalis; in these the ectopic beats reappeared after the injection of 29 per cent and 32 per cent, respectively, of the fatal dose for each animal (the minimum lethal doses were 0.84 and 0.94 cc., respectively).

tomed to restriction by the frequent taking of electrocardiograms during the three weeks following the operation.

The average dose required to produce a ventricular ectopic rhythm in the control animals that had been operated on was 0.45 cc., and in those with infarcts it was 0.35 cc. (table 3). In the presence of cardiac infarction, therefore, the tolerance of the animal to this effect of the drug is 22 per cent lower than that of the control. This is the same as the reduction in the tolerance to the fatal action.

C. Displacement of RT or ST Segment: In the electrocardiograms of human beings digitalis may cause displacement of the ST segment similar to that in coronary thrombosis. This has also been observed for the cat.[10] We found that the change sometimes occurs when the rhythm is normal but more frequently after a degree of poisoning which has induced a ventricular ectopic rhythm. The data were analyzed to determine whether digitalis is more likely to produce displacement of the RT segment in the infarcted heart than in the normal heart. The results show that the displacement was produced in 65 per cent of the twenty control animals and occurred only after the ventricular ectopic rhythm had appeared (chart 1 *D*). In those with infarcts it was about the same, 69 per cent after the ectopic rhythm had appeared (chart 1 *B*); but likewise in 24 per cent (seven animals) a distinct deviation of the RT segment also appeared earlier and occurred during the normal sinus rhythm (chart 1 *A* and *C*). In four of these animals, however, some displacement was present before ligation of the coronary artery; it became much more marked immediately after the operation and subsequently disappeared for a period of days, only to reappear during the injection of digitalis (chart 1 *A*). In other respects this group of seven animals yielded results similar to the average for the entire series of animals with infarction; i. e., the average size of the infarct was 5.35 sq. cm., the average blood pressure before the administration of digitalis was 147 mm. and the average fatal dose was 0.60 cc. per kilogram. These changes in the "take-off" do not always persist, being present in some beats and not in others, appearing in one tracing and disappearing in a subsequent one (chart 1 *A*). These changes represent the reestablishment, during injection of digitalis, of a temporary effect of occlusion, but their significance remains in doubt.

D. Blood Pressure: The mean blood pressures for the three groups (groups A, B and C) just prior to the beginning of the injection of digitalis were practically identical, 152 mm. for the normal animals, 155 mm. for those which had the control operation and 150 mm. for those with cardiac infarction.

10. DeGraff, A. C., and Wible, C. L.: Production by Digitalis of T-Wave Changes Similar to Those of Coronary Occlusion, Proc. Soc. Exper. Biol. & Med. **24**:1, 1926.

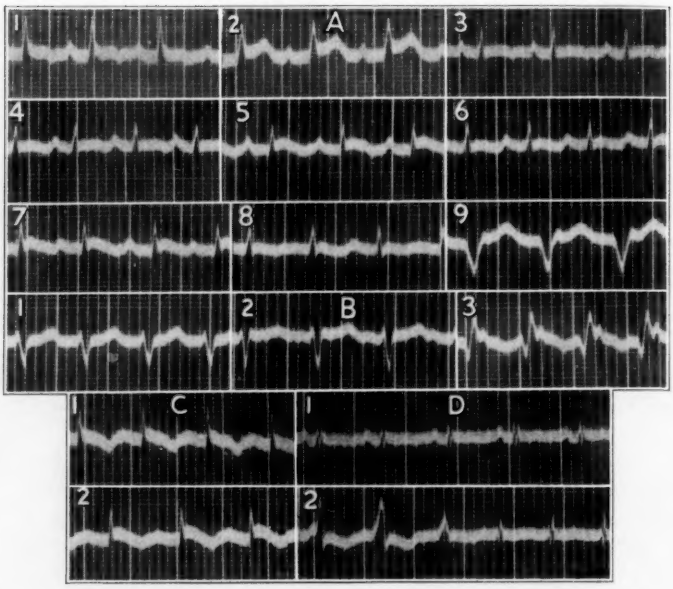

Chart 1.—Electrocardiogram (lead II) showing various effects of digitalis on the RT or ST segment. *A*, animal with infarction: *1*, before ligation of the coronary vessel; *2*, very high "take-off" seven minutes after ligation; *3*, disappearance of displacement of the RT segment on the eighth day after ligation; *4*, displacement still absent three weeks after ligation, just before the administration of digitalis; *5*, high "take-off" after the administration of 54 per cent; *6*, 58 per cent; *7*, 66 per cent; *8*, 75 per cent, and *9*, 80 per cent of the minimum lethal dose. Note the reestablishment by digitalis of the displacement of the RT segment produced by cardiac infarction, its appearance during sinus rhythm and its intermittent character with increasing doses of digitalis. *B*, animal with infarction: *1*, before the administration of digitalis—spontaneous ventricular tachycardia; *2*, after 80 per cent of the minimum lethal dose; *3*, high "take-off" after 88 per cent of the minimum lethal dose. Note the absence of the high "take-off" in idioventricular beats before the administration of digitalis and its presence during advanced poisoning; see also *A* 9. *C*, animal with infarction: *1*, before the administration of digitalis; *2*, after 70 per cent of the minimum lethal dose. Note the effect of digitalis in increasing the preexisting displacement of the RT segment. *D*, control animal: *1*, control tracing; *2*, after 81 per cent of the minimum lethal dose. Note the displacement of the RT segment in ventricular ectopic beats, but not in immediately subsequent supraventricular beats.

The typical change in the blood pressure of the cat during the course of the injection of a diluted tincture of digitalis by the technic used in these experiments exhibits two phases: (1) a gradual decline and (2) an abrupt collapse.

In the normal animal there was a progressive decline of the pressure, which began after an average of 0.25 cc. (0.04 to 0.46 cc.), or 32 per cent of the fatal dose, and the pressure continued to fall gradually to an average level of about 55 mm. (33 to 110 mm.), at which it was maintained for a period, after which it fell abruptly to 10 or 15 mm. just before the convulsion. The animal then ceased to breathe, or, as was more often the case, several wide fluctuations in pressure occurred before the heart beat and respiration ceased.

The fall in blood pressure did not seem to depend on the ventricular ectopic rhythm, and while a fall sometimes was first seen when the ventricular rhythm appeared, some decline usually occurred while the rhythm was still normal.

In the animal with infarction the changes in pressure were similar to those in the normal animal, the decline beginning after an essentially similar amount of the drug, 0.32 cc.[11] (0.02 to 0.48 cc., about 53 per cent of the fatal dose for the group with infarction), and continuing downward gradually; but instead of the protracted period of low blood pressure (average, 55 mm.) seen in the normal animal during the injection, the pressure in these instances fell abruptly much earlier in the course, from an average level of 90 mm. (41 to 128 mm.). This applied to the majority of animals; there were some in the group of normal animals (10 per cent) that behaved like those with infarction, and vice versa (33.3 per cent).

The characteristics of animals with infarcts of almost identical average size but with different types of blood pressure curves are illustrated in a comparison of the results for two groups, one of nine animals (infarct, 4.65 sq. cm.) showing normal blood pressure curves, the other of five animals (infarct, 4.58 sq. cm.) showing abrupt collapse of the blood pressure from a high level of 120 mm. or higher. The first group behaved in other respects practically like normal animals, requiring only 11 per cent less digitalis than normal animals to cause a ventricular ectopic rhythm and 3 per cent less to cause death. The second, on the other hand, required 29 per cent less to cause the ventricular rhythm and 39 per cent less to cause death.

The two phases of the change in blood pressure appear to be due to different mechanisms. The fact that the gradual decline of the blood pressure for the animal with an infarct begins after about the same

11. In view of the great individual variability, we believe that no significance can be attached to the difference between this figure and that for the normal animal.

amount of digitalis as for the normal animal suggests that the gradual fall is due to an extracardiac factor. This progressive decline is interrupted earlier in its course in the animal with cardiac infarction by reason of the greater susceptibility of this animal to cardiac collapse (ventricular fibrillation), which is probably the cause of the secondary abrupt fall in pressure.

Influence of Size of Infarct.—A. Fatal Dose: The size of the infarct was plotted against the size of the fatal dose of digitalis, and the result is shown in chart 2. By this method of examination a correlation is not clear. Of two animals with the smallest infarcts, one required the largest and the other the smallest fatal dose of digitalis. In two groups representing extremes of deviation from the average fatal dose for the normal animal, i. e., one requiring 97 per cent and the

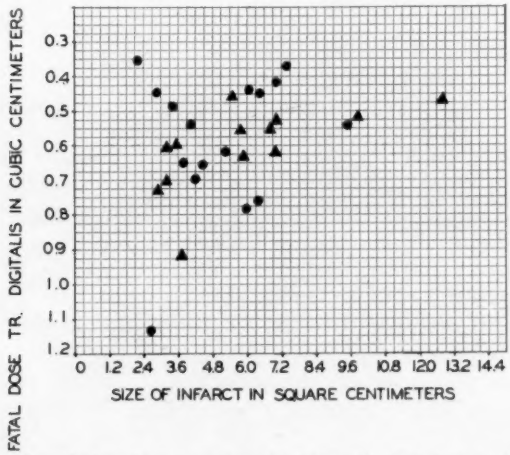

Chart 2.—Correlation chart for size of infarct and fatal dose of digitalis. The black triangle indicates animal treated with aminophylline; the black circle, animal not treated with aminophylline.

other 61 per cent of the normal fatal dose, the average sizes of the infarcts were practically identical, namely, 4.65 sq. cm. for nine animals in the first and 4.58 sq. cm. for five animals in the second group.

When, however, the small and the large infarcts were grouped separately, a relation was found to exist between the size of the infarct and the size of the fatal dose, as seen in table 5. This table shows that in one group (fifteen animals), in which the average size of the infarct was twice as large as that in another (fourteen animals), the increase in susceptibility was nearly doubled (1.8 times), the average fatal dose being 28 per cent less than that for the control in one and 16 per cent

TABLE 5.—*Influence of Size of Infarct on Susceptibility to Digitalis*

Infarcts	Number of Animals	Average Size of Infarct, Sq. Cm.	Average Dose, Cc. per Kg.	Reduction of Dose, Percentage of Control Dose
A. Fatal Dose				
None (controls)	12	....	0.76	..
Smallest	14	3.50	0.64	16
Largest	15	7.29	0.55	28
Smallest	5	2.72	0.66	13
Largest	5	9.29	0.49	36
B. Dose Causing Ventricular Ectopic Rhythm				
None (controls)	12	....	0.45	..
Smallest	13	3.48	0.35	22
Largest	13	7.10	0.35	22
Smallest	5	2.72	0.32	29
Largest	5	8.65	0.30	33

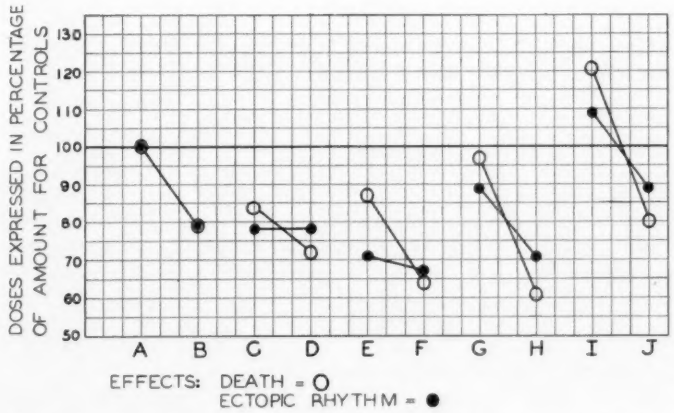

Chart 3.—Effect of infarction on the dose required to cause (*a*) death, indicated by white circle, and (*b*) ventricular ectopic rhythm, indicated by black circle. The doses are expressed as percentages of the average dose required to produce these effects in the control. *AB* indicates a comparison of twelve control animals (*A*), the average dose taken as 100 per cent, with twenty-nine animals with infarction (*B*). *CD* indicates a comparison of fourteen animals having the smallest infarcts (*C*) with fifteen having the largest infarcts (*D*). *EF* indicates a comparison of five animals having the smallest infarcts (*E*) with five having the largest infarcts (*F*). *GH* indicates a comparison of nine animals with infarction showing blood pressure curves similar to normal (*G*) with the group of five showing collapse of the blood pressure from a high level of 120 mm. or more (*H*). The average sizes of the infarcts in *G* and *H* were almost identical. *IJ* indicates a comparison of the five most tolerant animals in the control group (*I*) with the five most susceptible animals in the control group (*J*).

less in the other. In two smaller groups, in which the average size of the infarcts of one was about 3.4 times greater than that of the other, the increase in susceptibility was nearly trebled (2.7 times), the average

fatal dose being 36 per cent less than that for the control for the largest infarcts and 13 per cent less for the smallest infarcts.

B. Ventricular Ectopic Rhythm: As may be seen in table 5, the change in tolerance to the ventricular ectopic rhythm shows considerable irregularity and does not appear to depend on the size of the infarct.

The relation of changes in tolerance to the fatal action and to the production of the ectopic rhythm is illustrated in chart 3.

The abnormal ventricular rhythm which occurs as the result of coronary occlusion is also fairly independent of the size of the infarct. It occurred spontaneously in eleven of forty-two cats [3] in from two to twenty-one days after ligation of the coronary artery. These cases were represented throughout the range of sizes of infarcts, the average for the thirty-one animals without this rhythm being 5.66 sq. cm. and that for the animals with this rhythm being similar, 6.43 sq. cm.

Influence of Degree of Healing of Infarct.—There was no relation between the degree of healing seen on microscopic examination of the

TABLE 6.—*Relation of Fatal Dose of Digitalis to Degree of Healing of Infarct*

Degree of Healing of Infarct	Number of Cats	Size of Infarct, Sq. Cm.	Fatal Dose of Tincture of Digitalis, Cc. per Kg.
Advanced	4	5.75	0.52
Moderate	15	5.22	0.65
Slight	7	6.29	0.52

infarct and the fatal dose in twenty-six animals in which the infarct was sectioned (table 6). The criteria for the classification of the degree of healing were described in the previous report.[3]

It is interesting to note that all three degrees of healing were present in both large and small infarcts, although one might expect a small infarct to heal more rapidly than a large one. The smallest infarct in our series showed only a slight degree of healing.

COMMENT

The foregoing results show that the cat with a partially healed cardiac infarction requires about 25 per cent less digitalis to cause a ventricular ectopic rhythm than the normal animal and that this change is about the same for infarcts of widely different sizes.

There is approximately the same reduction of the fatal dose. This observation is contrary to that of Bellet, Johnston and Schecter [2] for cats but practically identical with their results for dogs. In the case of the fatal action the increase in susceptibility varies from 13 per cent in those with a small infarct to 36 per cent in those with a large infarct.

In the animals with infarction requiring a small fatal dose the blood pressure may fall abruptly from a high level of 120 mm. or more rather

than after a period at a low level of about 55 mm., as in those requiring a larger fatal dose.

Differences in the tolerance to digitalis may involve equally the fatal dose and that causing a ventricular ectopic rhythm, but when the entire group of animals is split up in order to reveal extreme differences in tolerance, the range of change tends to be greater for the fatal dose than for the ectopic dose (chart 3). This applies not only to animals with infarction (*CD, EF, GH*) but also to normal animals (*IJ*).

The mechanism by which cardiac infarction increases the susceptibility to digitalis is not known, but certain facts have thrown light on the following possibilities:

1. Reduction of the cardiac mass taking up digitalis
2. Reduction of the cardiac power to withstand the rapid rate of the ventricular tachycardia
3. The providing by the infarct of a region in which digitalis sets up abnormal impulses leading to ventricular tachycardia and fibrillation.

The first of these possibilities cannot be effectively defended, as the cardiac muscle takes up an extremely small proportion of the total amount of digitalis administered. Furthermore, perhaps an even larger mass of muscle is excluded from the circulation shortly after ligation of the coronary vessel, and at this time, as shown in other studies, no reduction in the fatal dose is demonstrable. The second possibility also seems unlikely as the sole explanation, as it fails to explain the fact that susceptibility is increased to the ventricular ectopic rhythm itself. This mechanism may play a part, since animals with the larger infarcts tolerate relatively less digitalis after this rhythm has been produced by the drug than do those with the smaller infarcts.

The third possibility is more in harmony with the existing facts. Accordingly, the increased susceptibility to a ventricular ectopic rhythm would be due to the action of digitalis in an abnormal region of the heart from which arise stimuli leading to ventricular tachycardia and fibrillation. This receives support from the fact that the susceptibility to the ventricular rhythm as well as to the fatal action is increased and that an extremely small and a very large infarct may cause approximately the same reduction in tolerance to the ectopic rhythm, indicating that the essential factor is the presence of an abnormal focus rather than its size. The abnormal area from which impulses might arise would not be the region in which the circulation is completely abolished but an area of muscle around or in the infarct in which healing has taken place and in which the circulation is impaired. This is suggested by the fact that the increased susceptibility to the fatal action develops only after a degree of recovery from the complete occlusion, no change

being in evidence shortly [12] after the vessel is ligated. It is conceivable that the abnormally susceptible region is the rest of the ventricle, rather than any special focus in or about the infarct, although this involves the assumption that the hyperirritable state of the ventricle develops during the period of recovery rather than immediately after closure of the coronary vessel, when the strain on the ventricle is probably the greatest.

Clinical Significance.—The value of digitalis in coronary thrombosis does not come within the scope of this study. It is well known that relatively few patients with coronary thrombosis require digitalis, but our results lend no support to the belief that the use of digitalis is attended by any special hazards in these cases. The landmarks which have been examined have not appeared to be materially changed. Thus, the range of variations in tolerance, especially tolerance below that of the average for the group, is practically the same as that for normal animals. Also, the ventricular ectopic rhythm, which appears after about 60 per cent of the fatal dose for normal animals, is produced by a similar percentage of the dose that was fatal for the group with infarction. One factor which cannot be investigated in the animal is the range between the full therapeutic and the toxic action (margin of safety). If, by any chance, the susceptibility to the therapeutic action were to remain unchanged, the margin of safety would be reduced; but concerning this we have no data.

As matters stand, the experimental results may be taken to signify that in order to attain the usual objective it would be safer to use about 25 per cent less digitalis for patients with coronary thrombosis than for those without it. The reduction of the dose may be somewhat less for patients with a small infarct and somewhat more for those with a large infarct. Should one fail to take this factor into account when massive doses are given for rapid digitalization, undoubtedly toxic symptoms would result. However, with the slower methods, in which symptoms serve more effectively as a guide to dosage, a 25 per cent diminution in tolerance or its converse, a 25 per cent increase in the dose, might readily escape detection.[13]

SUMMARY AND CONCLUSIONS

In the present study of fifty cats the effect of digitalis on the control animal is compared with that on the animal three weeks after experi-

12. We have no data on the tolerance to ventricular tachycardia shortly after the occlusion, the previous studies having involved consideration of only the fatal dose.

13. Wyckoff, J.; Gold, H., and Travell, J.: The Importance of Differences in the Potency of Digitalis in Clinical Practice, Am. Heart J. **5**:401, 1930. Gold, H., and DeGraff, A. C.: Studies on Digitalis in Ambulatory Cardiac Patients: IV. Newer Principles of Digitalis Dosage, J. A. M. A. **95**:1237 (Oct. 25) 1930.

mental ligation of a coronary vessel with respect to the following points: the fatal dose, the dose necessary to produce a ventricular ectopic rhythm, the effect on the blood pressure, the changes in the RT segment of the electrocardiogram and the degree of healing of the infarct.

Previous studies have shown that within the first twenty-four hours after the experimental production of cardiac infarction the tolerance to digitalis is the same as that of the normal animal (cat and dog).

In the presence of a partially healed infarct the cat (as well as the dog) is more susceptible to digitalis than the normal animal, requiring only about three-fourths as much digitalis as the normal animal to cause (*a*) a ventricular ectopic rhythm and (*b*) death.

The larger the infarct, the more susceptible the animal; but many exceptions to this rule were observed, and some of the most susceptible animals had the smallest infarcts.

Treatment with aminophylline appeared to exert no effect on the tolerance to digitalis in cardiac infarction.

There is some indication that digitalis may cause displacement of the RT segment in the electrocardiogram more readily in animals with cardiac infarction than in the normal animal.

Differences in tolerance may involve equally the fatal dose and that required to cause a ventricular ectopic rhythm, but the range of change tends to be greater for the former than for the latter. This appears to be true of differences in tolerance among apparently normal animals, as well as among those with cardiac infarction.

The facts indicate that increased susceptibility to digitalis in cardiac infarction may be due to a change in the properties not of the whole heart but of an area with impaired circulation within the zone of the infarct, from which abnormal impulses arise as the result of the administration of digitalis and precipitate ventricular tachycardia and fibrillation.

SUBCUTANEOUS ADMINISTRATION OF OXYGEN

THOMAS SIMPSON, M.B., CH.B.*
LEEDS, ENGLAND
AND
M. HERBERT BARKER, M.D.
CHICAGO

The subcutaneous administration of oxygen first became popular in Europe after the introduction of a machine built by Dr. Bayeux,[1] of Paris. Since then there has been much controversy as to the value of this form of therapy, but little attention has been paid to it in America and England until recently. The workers on the subject can readily be divided into two groups: first, those who believe its use to be of value, basing their conclusions on clinical observation unconfirmed by laboratory procedure, and, second, those who declare it to be useless, their conclusions being based entirely on experimental data.

One cannot deny that if clinical benefit is seen from the injection of oxygen subcutaneously, there must be some basis for its use. Workers claim benefit from its use in such divers conditions as distemper, burns, pneumonia, postoperative nausea and vomiting, heart failure, pulmonary tuberculosis, thrombosis and embolism, pulmonary edema, toxemia, septicemia, uremia, convulsions and asphyxia of the new-born; in fact, Simon [2] and Kirk [3] gave as indication for its use any condition complicated by symptoms of anoxia and asphyxia. Most of those in favor of the administration of oxygen subcutaneously admit that the amount injected is not sufficient to alter materially the oxygen content of the blood, yet in all the conditions enumerated what other common factor

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* Fellow in Medicine, Passavant Memorial Hospital, Chicago.

From the Department of Experimental Medicine of Northwestern University Medical School.

The Linde Air Products Company donated the oxygen and nitrogen for use in these experiments.

This work was made possible in part by a grant from the Council on Physical Therapy of the American Medical Association.

Read before the Section on Pathology and Physiology at the Eighty-Eighth Annual Session of the American Medical Association, Atlantic City, N. J., June 11, 1937.

1. Bayeux, R.: Bull. Acad. de méd., Paris **87**:176, 1922.

2. Simon, Oliver B.: Clin. Med. & Surg. **40**:155, 1933; Anesth. & Analg. **13**:233, 1934.

3. Kirk, T. S.: Brit. M. J. **2**:195 (Aug. 4) 1928.

is there that can be benefited by the subcutaneous administration of oxygen?

As we are particularly interested in the use of this method in pneumonia, in which great benefit is claimed, we shall confine ourselves to a discussion of this subject.

Kirk [3] said that the early administration of oxygen subcutaneously in cases of acute lobar pneumonia gave uniformly good results, the crisis coming on rapidly. He showed charts to demonstrate this. He cited one instance in which he gave a large dose of oxygen subcutaneously four hours before death to a patient suffering from double pneumonia. At postmortem examination, four hours later, there was no rigor mortis, and the blood that issued from the anterior cutaneous incision was bright red. There was no statement as to the presence or absence of cyanosis before death. Considering the rapidity with which blood, even after death, takes up oxygen, one must be skeptical of this observation. Kirk said he believed that oxygen given subcutaneously acts by helping to kill the pneumococcus and at the same time by counteracting the toxemia. He stated that "subcutaneous injections of oxygen, besides being of great use in cases of pneumonia, are of value in all cases of anoxia."

Lipkin and his associates [4] studied the effect of the subcutaneous injection of oxygen on the hemolytic, complimentary and specific antibody potency of the serum of dogs. They found the first two values to be reduced and the last to be raised from sixteen to fifty days after the commencement of such treatment. However, the alteration in the agglutination titer is of such small magnitude as hardly to warrant this conclusion. Their experiments were carried out on five dogs (two being controls), and the amount of oxygen given daily varied from 10 to 30 cc. per kilogram of body weight. They suggested that the injection of oxygen might be of practical use in the treatment of acute and chronic diseases and for the preparation of more potent specific serums. However, in the treatment of pneumonia the disease had run its course before the injection of oxygen could have had any of the effects mentioned.

It is of interest here to note that Evans [5] reported on one patient with pneumonia whose cyanosis failed to clear up completely with the nasal administration of oxygen but did so when oxygen was given subcutaneously. Neither the amount of oxygen in the blood nor the amount of oxygen injected was reported.

Simon [2] remarked that the efficacy of the subcutaneous administration of oxygen in pneumonia seems unbelievable, considering the large

4. Lipkin, J. J.; Podvalny, P. B., and Grintzevic, O. M.: Gior. di batteriol. e immunol. **13**:661, 1934.

5. Evans, John H., and Durshordwe, C. J.: Anesth. & Analg. **11**:193, 1932.

amount required by the inhalation method. To explain this he said that in pneumonia the amount of deficiency in oxygen saturation is presumably in proportion to the difference between the supply and the demand and that this is usually a small amount. He claimed that in pneumonia distress and anxiety are relieved after the administration of oxygen subcutaneously.

In support of the contention that oxygen injected subcutaneously is readily utilized by the body, he measured the basal metabolic rates of two hyperthyroid patients before and directly after the injection of 200 and 300 cc., respectively, of oxygen subcutaneously. The latter amount caused the basal metabolic rate to fall as much as 18 per cent in ten minutes, the return to the former level taking as long as ten days. He said, "This indicates that there is an indirect effect on the anoxia due to the slowing of the metabolism processes." However, if one takes into consideration the ends that normally arise in determining basal metabolic rates, these observations must be regarded as of doubtful value.

It may be assumed, then, that Simon concluded that the subcutaneous administration of oxygen actually compensates for the disproportion between the supply and the demand of oxygen. This disproportion must be small indeed, considering that in the normal animal subcutaneous oxygen is absorbed at the rate of 0.6 to 1.2 cc. per minute.[6] Singh [6] and Campbell [7] also found that the absorption of oxygen became nil, or nearly so, at the end of from one to one and a half hours after the injection because of the lowering of the tissue tension of the injected gas. However, these experiments were carried out on the normal animal, and presumably if the animal's demand for oxygen were much greater, the rate of absorption from the tissues might be correspondingly increased. With this fact in mind, we carried out the experiments to be described.

In a series of experiments on the effects of anoxia on the chemistry of the blood, reported on elsewhere,[8] we found that oxygen could be withheld from the inspired air of normal dogs with impunity until a level of from 4 to 4.5 per cent was reached, when critical symptoms of anoxia were noted. Death occurred when there was about 3 per cent of oxygen in the inspired air. At these low levels the oxygen saturation of the arterial blood was found to be approximately 30 per cent. The demand for oxygen at these low levels should be sufficient to lead to utilization of some of the oxygen injected subcutaneously.

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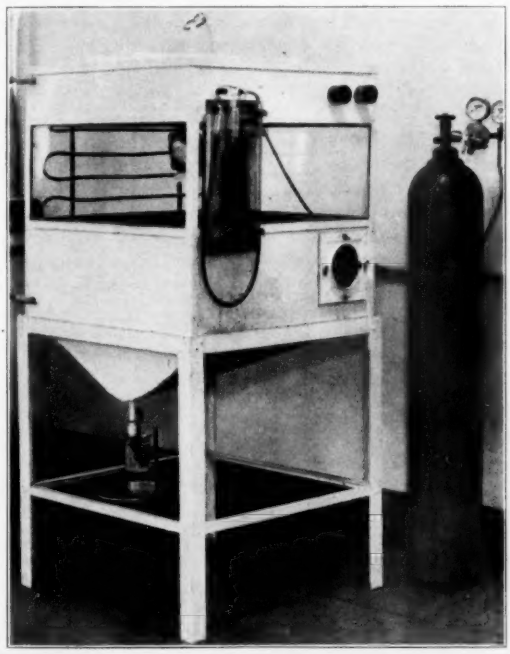
6. Singh, I.: Quart. J. Exper. Physiol. **22**:193, 1932.

7. Campbell, J. A.: J. Physiol. **59**:1, 1924.

8. Simpson, Thomas, and Barker, M. Herbert: Studies in Prolonged Anoxia, in Report on Epilepsy, Ann Arbor, Mich., Edwards Brothers, Inc., 1936, pp. 441-473.

METHOD

To carry out the following experiments we used a miniature oxygen chamber (figure). The chamber is of steel and glass and in two parts. The upper part, measuring 2 feet and 6 inches (76 cm.) in every dimension, can be raised from the lower part. When lowered it rests on a soft rubber cushion set in a trough in the lower part; this acts as an air seal. Inside the upper part (the chamber proper) and in the left window can be seen a set of cooling coils, and in the upper part at the right side (out of sight) is a tray of soda lime. The Muter "Telaire" apparatus on the right window records temperature and humidity. The various



The oxygen chamber is of steel and glass and measures 30 by 30 by 30 inches (76 cm.). It is closed when resting on the sponge rubber in the trough of the steel table, 36 inches (91.5 cm.) high. The chamber can be separated from the base by a pulley, which hooks into a ring on the top, thus permitting admission or removal of animals. The bottom of the table is equipped with a trap drain. Note the vents for conditioning the atmosphere, the cooling coils and the instruments for gas analysis. The small trap-door at the right permits feeding, obtaining samples and giving medication, as in the chamber of Thalheimer. If an animal board is placed at this trap, the animal's head can be kept in the chamber in the conditioned atmosphere while the body remains outside, permitting the drawing of arterial blood and other procedure. The chamber accommodates one large dog, two small dogs or cages for twenty-four rats.

parts seen are for admitting gas and for drawing off samples of the contained air for analysis. Between the upper and the lower part is a complete floor of firm fine mesh wire. In the lower part can be seen a drain, which has a water seal at its most dependent point. This provides for the draining away of excreta and condensed water.

At the right side of the upper part can be seen a rubber cuff encircling a circular door; through this the dog's head was inserted into the chamber so that it breathed only the air in the latter when it was necessary to bring the animal's body outside the chamber. The dog's body rested on a trough outside. With this method samples of blood could easily be drawn from the femoral artery without disturbing the dog. Oxygen was administered subcutaneously by means of a two way pump connected with a large reservoir of oxygen. The pressure exerted during the injection of oxygen was estimated and was never greater than that advised by Simon,[2] i. e., 40 Gm. per square centimeter. The concentration of oxygen inside the chamber was lowered by flowing in nitrogen.

We felt that these conditions were entirely satisfactory, since the dogs used were normal and the respiratory apparatus was in no way interfered with. Also, the temperature, humidity and composition of the air breathed could be carefully controlled. Arterial blood was drawn under oil from the femoral artery and immediately analyzed as to oxygen content and capacity by the method of Van Slyke and Stadie.[9] To perform these experiments it was necessary to anesthetize the dogs. We chose soluble barbital for the anesthetic because of its slight depressant action on the respiratory center. We also gave it in small doses, i. e., from 150 to 175 mg. per kilogram of body weight.

PROTOCOL

In a preliminary experiment, to see if there was any gross evidence of absorption of oxygen from the subcutaneous tissues in the presence of anoxia, we ballooned a dog's skin with as much oxygen as possible, paying no regard to the amount injected. Then we put the dog into the chamber and reduced the oxygen content of the inspired air to 4 per cent in the course of five hours. We could not detect any external evidence of absorption of the oxygen, nor was cyanosis prevented.

In the first experiment, with the dog in the chamber, we lowered the oxygen concentration of the inspired air gradually to 6 per cent over the course of two and a half days, so as to give the dog time to become acclimated to low oxygen tension. At the end of this time the dog was given soluble barbital (sodium barbital) in the proportion of 175 mg. to 1 Kg. of body weight. After the animal had been anesthetized its head was inserted into the chamber, as previously described. Then 1,500 cc. of oxygen was injected subcutaneously, and the oxygen content of the inspired air was lowered to 3 per cent over the course of two and a half hours. Blood was drawn from the femoral artery before the start of the experiment as a control at 6 per cent oxygen tension and before and after the subcutaneous administration of oxygen. The dog died.

Table 1 shows that the oxygen content of the arterial blood did not change after the injection of oxygen subcutaneously. Also, we observed at the time that the symptoms of respiration and cyanosis did not alter, nor was there any external evidence of absorption of the injected oxygen, except perhaps in the cervical region. The only difference noted was that the percentage of oxygen desaturation

9. Van Slyke, D. D., and Stadie, W. C.: J. Biol. Chem. **1**:49, 1921.

of the arterial blood was less after the injection of oxygen, i. e., 10.8 per cent, as compared with 16 per cent before. This, we thought, was due to an error arising in the drawing of the blood, as is borne out by the discrepancy between the degree of anoxia and the percentage of desaturation of the arterial blood. However, to be absolutely certain we repeated the experiment. A second dog was similarly acclimatized after a control study of the oxygen content of the blood and anesthetized with soluble barbital. When the oxygen content of the inspired air was 5 per cent, arterial blood was drawn, and 896 cc. of oxygen was injected subcutaneously; then at the end of two and one-fourth hours arterial blood was drawn again, the oxygen content of the inspired air being maintained at 5 per cent during this period.

Table 2 shows that the oxygen content of the arterial blood remained the same before and after the subcutaneous injection of oxygen. The symptoms,

TABLE 1.—*Data for the First Dog.*

	Oxygen in Inspired Air, %	Arterial Blood		
		Oxygen Content, %	Oxygen Capacity, %	Desaturation, %
	21	20.30	21.66	6.7
		20.31	22.17	8.4
	6	16.74	20.74	19.3
Before injection of oxygen	5	21.05	25.05	16.0
After injection of oxygen	3	20.31	23.90	10.8

TABLE 2.—*Data for the Second Dog*

	Oxygen in Inspired Air, %	Arterial Blood		
		Oxygen Content, %	Oxygen Capacity, %	Desaturation, %
	21	18.51	18.93	2.2
		17.43	18.87	7.6
Before injection of oxygen	5	8.16	19.96	59.1
After injection of oxygen	5	8.16	19.52	58.2

respirations and cyanosis did not improve; in fact, the respiration became deeper and more labored, and again there was no external evidence of the utilization of the injected oxygen. Since the percentage of desaturation of the arterial blood remained unaffected, the observation in the first experiment was in all probability a technical error. There remained the questions as to whether the acclimatization of the dogs affected the experiment and as to whether the oxygen levels were too low for absorption of the injected oxygen to take place. To answer these questions, in the next experiment we drew a control sample of arterial blood and then anesthetized the dog as before with soluble barbital. The dog's head was placed in the chamber, and the oxygen content of the inspired air was reduced to only 8.6 per cent in three hours. Arterial blood was drawn from the exposed femoral artery, and then 1,250 cc. of oxygen was injected subcutaneously. At the end of two hours another sample of arterial blood was drawn, the oxygen content of the air remaining constant at 8.5 per cent during this period.

Table 3 shows that the oxygen content of the arterial blood did not alter and that the percentage of desaturation was not materially affected. There was

little if any absorption of the injected oxygen, judging by the external appearances and crepitus of the subcutaneous tissues, nor did the symptoms and cyanosis alter. The dog winced and groaned as the oxygen was being injected, and the respirations became deeper, but we assumed that this was entirely reflex.

As we had not met with success in the previous experiments, it was deemed advisable to evaluate the relative merits of oxygen administered subcutaneously and by inhalation. The dog used in the last experiment was put into the chamber after having had approximately 1,200 cc. of oxygen injected subcutaneously and the attempted injection of an additional 200 cc. intramuscularly. The oxygen tension in the chamber was lowered to 7 per cent in the course of three and three-fourths hours and to 3 per cent in the subsequent hour. At a tension of 4.5 per cent of oxygen in the inspired air the dog was restless, cyanosed and extremely dyspneic, and at a tension of 3 per cent it was unconscious and about to die, in spite of the large volume of oxygen present subcutaneously. The respiration slowed and finally ceased, and at this point the dog was taken out of the chamber. He took two or three breaths, and the mucous membranes, which were black, turned bright red. At this point arterial blood was drawn, and the oxygen content was found to be 10.3 per cent. On referring to table 3,

TABLE 3.—*Further Data for the Second Dog.*

	Oxygen in Inspired Air, %	Arterial Blood		
		Oxygen Content, %	Oxygen Capacity, %	Desaturation, %
	21.0	18.98	21.24	10.6
Before injection of oxygen	8.5	10.33	19.00	45.6
After injection of oxygen	8.5	10.24	19.32	47.0

which presents data for the same dog, it is found that an arterial oxygen content of 10.33 per cent corresponds to a concentration of 8.5 per cent of oxygen in the inspired air. The dog was unconscious for about fifteen minutes, but he subsequently recovered and was perfectly well the next day.

RESULTS

This experiment shows how rapidly the blood takes up oxygen from the air when the need for it is great. Surely this indicates the marked advantage of the inhalation over the subcutaneous method of administering oxygen if adequate pulmonary surface is available when oxygen is urgently needed. The oxygen in the dog's tissues and muscles, although far in excess of that used clinically for human beings, was totally inadequate, whereas a few breaths of ordinary air was sufficient to restore the animal. It seems evident from these experiments on normal anesthetized dogs that at the time when one would most expect subcutaneous oxygen to be utilized, there was no supporting evidence from symptomatology and oxygen determinations. Other workers [10] have stated similar conclusions.

10. Spehl, P., and Lemort, A. C.: Compt. rend. Soc. de biol. **98**:1262 (May 4) 1928. Davies, H. W., and Rabinovitch, M.: J. Physiol. **64**:xxxviii, 1927.

COMMENT

Since the volume of oxygen given to the experimental animals was far in excess of that advised for human beings, it is probable that when there is a severe degree of anoxia, such as is encountered in pneumonia, oxygen given subcutaneously cannot materially effect the oxygen content or the percentage of oxygen desaturation of the arterial blood; in other words, its benefit, if actual, is not derived from its power to oxygenate the blood.

If this is so and if the rate of absorption of oxygen from the subcutaneous tissues is so slow, it is difficult to conceive what benefit this method can have. Even if the oxygen somehow neutralizes the toxins in pneumonia, as was suggested by Kirk, why may the subcutaneous injection of oxygen seem to be of benefit in other divers conditions, such as heart failure, in which presumably toxemia is absent? The work of Lipkin and his associates [4] raised the question of the stimulation of the formation of specific antibodies following the subcutaneous injection of oxygen. This is not likely to be a factor in pneumonia (as stated previously); however, we are investigating this point further. Singh [6] has shown that the ability of the lungs to saturate blood with oxygen is about fifteen or twenty times greater than that of the whole subcutaneous region. This point is well brought out in our last experiment. Finally, the fact that in pneumonia the percentage of oxygen desaturation of the arterial blood and its response to oxygen therapy are of prognostic significance seems to be overwhelming evidence in favor of the conclusion that the oxygen is of benefit solely for its power to oxygenate the blood. More critical evidence is needed before the subcutaneous injection of oxygen can be accepted as a sole means of combating systematic anoxia. The work presented in this paper does not exclude the possible value of the subcutaneous injection of oxygen in cases of extreme anoxia as an adjunct to other standard forms of oxygen therapy, nor is the treatment of local conditions by injection of oxygen covered.

CONCLUSIONS

Oxygen given subcutaneously to anoxic dogs in amounts far greater than that advised for adult human beings failed to alter the oxygen content or percentage of desaturation of the arterial blood.

No evidence of absorption of subcutaneous oxygen by the anoxic animal was obtained even when it was urgently needed.

The great efficiency of the inhalation method is emphasized by these experiments.

ABSTRACT OF DISCUSSION

DR. HENRY C. SWEANY, Chicago: I am wondering what the effect is in surgical conditions. This method has been used in thoracoplastic operations

apparently with slight temporary improvement of the dyspnea. I wonder how Dr. Barker would explain that.

While physiologists do not seem to be able to explain this action clinicians seem to observe a temporary improvement after its administration. I should like to have some clinical discussion of this subject, if there are any clinicians here who have had experience with it.

Dr. Clyde Brooks, New Orleans, La.: We are indebted to the essayist for an excellent paper. From the standpoint of physiology, the result is just what would be expected. I am utterly at a loss to see how the subcutaneous injection of oxygen could be of any benefit in a case of pneumonia or any other clinical condition in which oxygen want is an outstanding feature. If there is any benefit, it seems to me it must be due to the stimulation of reflexes by the local action of the oxygen or some other similar action.

Dr. Virgil Moon, Philadelphia: I cannot take this subject up from the standpoint of internal medicine, but perhaps one or two observations from the standpoint of pathologic physiology may be pertinent. Tissue anoxia becomes a major feature in many clinical states associated with intoxication after burns, during the course of severe acute infections or after extensive trauma or surgical intervention. These conditions may lead to a type of circulatory deficiency usually designated as shock. Anoxia is one of the major factors in the vicious circle, a self-perpetuating mechanism by which the circulatory failure becomes more and more marked. The circulation becomes progressively less able to maintain delivery of oxygen to the tissues. It seems to me that the paper by Dr. Barker bears directly on that point. One of the major difficulties in breaking the vicious circle and in restoring physiologic efficiency is that of getting oxygen to the tissues. The lungs are partially incapacitated by virtue of the engorgement and edema which have developed in them. Their function perhaps can be reenforced or aided by the administration of oxygen by some other route. I had not thought or heard of the subcutaneous introduction of oxygen as a possible means for accomplishing that purpose. Giving oxygen in an oxygen tent and, as has been suggested by Dr. Bullowa, by inhalation under pressure have been considered. It seems that the introduction of oxygen by the subcutaneous route offers another means of attack on the anoxia which may develop in a wide variety of clinical conditions.

Dr. J. H. Bacon, Peoria, Ill.: I am not a member of this Section; I am a surgeon. Years ago, cows with garget were treated by injecting oxygen through the duct of the nipple, and farmers thought that they noted a definite improvement in the condition of the cows. Then later the same method was used for women with toxemia of pregnancy, by injecting pure oxygen into the breasts. About twenty years ago I had two patients with eclampsia who were given oxygen, all the breasts would hold, over a period of an hour; both of them seemed to improve and, they both recovered. I have not been using this method in recent years because other methods of treatment of eclampsia have been introduced since then.

Dr. M. Herbert Barker: I appreciate these questions because they are the questions that are being raised by many. The motive for carrying on this type of experimental work is to try to remove some of the uncertainty, confusion and perhaps delusion from the subject of the subcutaneous administration of oxygen.

Members of the medical profession are becoming more and more oxygen conscious, and if the subcutaneous administration of oxygen is an answer to the problem of systemic anoxia, then it is the simplest and least expensive method

of treatment. However, according to the literature and according to the facts brought out in this discussion, so many conditions are reported as being aided by the subcutaneous administration of oxygen that the method does not seem sound. Better physiologic reasons must be found for the apparent benefit in these diverse conditions before the method and the small volume of gas used can be accepted as the explanation.

With regard to the injection locally, which Dr. Brooks has discussed, it is our opinion that nothing but reflex stimulation is the cause of some of the temporary and rather acute benefit that is seen. I am doubtful that this is a good answer, but it is impossible to explain it in any other way as yet. Certainly it is not explained from the standpoint of relief of arterial desaturation. The fact that the average person requires from 300 to 500 cc. of oxygen a minute and the fact that from 300 to 500 cc. is introduced once a day subcutaneously render such a method useless to the patient who really needs oxygen. So if results are being obtained with these small doses, they are being obtained in some other way than by the correction of blood oxygen desaturation, as our work tends to show.

I am anxious to support Dr. Moon's discussion in relation to peripheral vascular states in shock, in coronary disease and in postoperative states. In some institutions, as mentioned by Dr. Waters, it has been found that about 75 per cent of all oxygen is given by surgeons. They find it is of tremendous benefit to their patients postoperatively. I am anxious to have the work that we are reporting not stand in any way against the subcutaneous administration of oxygen in conditions in which it can possibly do any good. My experience has been that there are possible uses for it as an adjunct to the inhalation route, but large doses must be given. Administering from 5 to 15 liters under the fascia lata, where it is under pressure and can diffuse into the muscle and where there is a rich blood supply, has seemingly been of real benefit to the severely anoxic patient, for example, the severely anoxic patient with pneumonia, for whom the inhalation route is not sufficient. A large volume of oxygen may be burned every three or four hours. Such an adjunct volume, administered subcutaneously, is quantitatively adequate to do something for arterial desaturation. But this volume is far larger than is customarily given. I feel that conditions of this sort should be studied further. Certainly local conditions, such as the gas gangrenes and some skin grafts, may be benefited by local injection of oxygen, but these are local conditions, not systemic anoxia.

ROLE OF ANOXIA IN PRODUCTION OF EPILEPTIFORM SEIZURES

WITH STUDIES OF THE ACID-BASE EQUILIBRIUM

THOMAS SIMPSON, M.B., CH.B.*
LEEDS, ENGLAND
AND
M. HERBERT BARKER, M.D.
CHICAGO

For many years different workers have attempted to show that voluntary hyperpnea can produce seizures in a patient with epilepsy. Numerous theories have been advanced for the mode of action, all of them being connected either with changes in the concentration of specific ions in the blood or with alterations in the acid-base equilibrium. In voluntary hyperpnea a state of alkalosis is encountered. Because of this, Lennox [1] suggested, for the first time, that anoxia may play a part in the production of seizures, in that in alkalosis the blood gives up oxygen less readily, thereby causing oxygen lack in the tissues.

On the basis of this premise it should be possible to predict the occurrence of seizures as the result of voluntary hyperpnea. A review of the literature shows a lack of agreement as to the incidence and mechanism of the production of seizures by hyperventilation or anoxia.[2] To test the rôle of anoxia in producing seizures Lennox and Cobb caused patients to hyperventilate in air poor in oxygen. Seizures were most readily induced in patients with frequent petit mal attacks, but there

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The Linde Air Products Company donated the nitrogen for use in these experiments.

* Fellow in the Department of Experimental Medicine, Northwestern University Medical School.

From the Department of Experimental Medicine and the Department of Nervous and Mental Diseases, Northwestern University Medical School.

This study was made possible by grants from the Minnie Frances Kleman Fund and from the Council on Physical Therapy of the American Medical Association.

1. Lennox, W. G., and Cobb, S.: Epilepsy, Harvard Medicine Monograph, Baltimore, Williams & Wilkins Company, 1928, vol. 14.

2. Fog, M., and Schmidt, M.: Hyperventilation Experiments During CO_2 and O_2 Inhalation in Patients with Convulsions, J. Neurol. & Psychopath. **12**:14-23, 1931. Baudouin, A., and Schaeffer, H.: L'épreuve de l'hyperpnée, Rev. neurol. **1**:445-473, 1933. Petersen, C. J. N.: Contribution à la pathogenèse de l'èpilepsie et à la genèse d'une attaque épileptique provoquée par hyperventilation, Compt. rend. Soc. de biol. **106**:580-583, 1931.

was failure to obtain them in patients suffering from grand mal seizures. Lennox [1] found that the degree of anoxia sufficient to induce an attack would be inadequate if the respired air contained an increased percentage of carbon dioxide or if the patient was in a state of acidosis.

The results of anoxia depend on its degree, suddenness of production and duration.[3] If the oxygen deficiency is of a sufficient degree, the acid products formed in the tissues pass into the blood and overcome the normal alkalinity, with resulting marked acidosis. Coincident with this acidosis, the respiratory center is depressed, and carbon dioxide in conjunction with oxygen is necessary to stimulate it. This change of state from one of pure anoxia to one of asphyxial acidosis occurs when the oxygen content of the respired air is reduced to 8 per cent.[3a] In conditions of moderate anoxia, the bicarbonate level of the plasma falls, the decrease being accompanied chiefly with an increase in the chloride content of the serum and partly by an increase in the protein content. The p_H increases moderately. In some cases there may be a diminution in total base so as to help compensate for the loss of carbon dioxide by hyperventilation. There is a reduction in the phosphate content.[4] If the anoxia is carried further, acids, such as lactic acid, accumulate in the blood, the p_H falls and the bicarbonate content of the plasma diminishes markedly. This is the condition of asphyxial acidosis.

Thus, in anoxia there are definite changes in the acid-base equilibrium which are not seen in epilepsy before or after a seizure.[5] During an attack there is a state of acidosis which is similar to the asphyxial acidosis of severe anoxia.[6] In an epileptic seizure, however, the acidosis is the result and not the cause of the attack. One must not lose sight of the fact that in the space of a few minutes the acid-base equilibrium may be totally disturbed, as in voluntary hyperpnea.

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A review of the literature caused us to feel that the nature and short duration of the experiments reported, the apprehension of the patient, the frequent occurrence of phenomena of motor excitation, fainting spells and the beneficial effect of carbon dioxide in reducing the incidence of seizures cannot be ascribed to anoxia per se. Therefore, we decided to subject patients with epilepsy to the effects of prolonged anoxia to see at what percentage of oxygen tension in the inspired air we could, if possible, induce seizures.

METHOD

A double oxygen chamber was used for these experiments, but nitrogen instead of oxygen was pumped in to reduce the oxygen content of the inspired air. The patients (thirteen in all) lived in the chambers and had much freedom. They were allowed to get up and walk about, and as there was a communicating door between the two chambers they could talk to each other, play cards and relieve the monotomy in other ways. The humidity, temperature and oxygen content of the air were under perfect control. In other words, the patients were free from the apprehension that must occur in any rebreathing experiment. This, we feel, was important. In some cases the diet was planned so as to regulate the intake of phosphorus, sulfur and chlorides and to control further the studies of the acid-base equilibrium. A chart of the water balance was kept so that the twenty-four output of the various ions could be calculated and the mineral balance thus determined. The duration of the patient's stay in the chamber was thirty-six hours, except in the case of three patients, two of whom were released at their own request because they felt ill and one who stayed in for four days. As a routine procedure blood was drawn under oil from the radial artery on the day of the patient's admission to the chamber, and then the oxygen content of the inspired air was lowered to 17 per cent and held there for about twelve hours. This was found adequate to prevent "mountain sickness." In the next eighteen hours the oxygen content was lowered gradually to 10 per cent and in the subsequent six hours to as low as was thought safe for the patient, the lowest being 7 per cent. At this point blood was again drawn from the radial artery. One patient, J. A., who was in the chamber four days, respired the following atmospheres: first day, an average of 16 per cent oxygen; second day, 14 per cent oxygen for twelve hours, and 12 per cent oxygen for twelve hours, and third day, 11 per cent oxygen for eighteen hours. In the subsequent five hours the percentage of oxygen was lowered to 9. Considerable difficulty was often encountered in drawing the final specimens because of the collapsed condition of the arteries. For this reason the percentage of oxygen desaturation of the arterial blood recorded in the charts is not as great in some cases as it should be. If the patient had a seizure during his stay in the chamber, arterial blood was drawn immediately. The carbon dioxide content of the air in the chamber never rose above that of the normal atmosphere of a room, even though there was no soda lime in the air circuit. The carbon dioxide content was kept down by continuous dilution with nitrogen. The oxygen of the air in the chamber was analyzed every one or two hours by means of a Haldane analyzer. The blood in all cases was analyzed for the oxygen content; oxygen capacity; hematocrit reading; carbon dioxide, total halide, sulfur, phosphate and total protein contents, and in some cases cholesterol and phenol contents.

The oxygen content of the arterial blood was determined by the method of Van Slyke;[7] the carbon dioxide content, by the method of Van Slyke and Cullen;[8] the total halide content, by the method of Whitehorn;[9] the total protein content, by the combined methods of Howe and Wu and Koch and McMeekin, as described by Hawk and Bergeim;[10] the inorganic phosphate contents of the blood and urine, by the methods described by Fisk and Subbarow;[11] the inorganic sulfate contents of the blood and urine, by the method described by Hoffman and Cardon;[12] the cholesterol content of the blood, by the method of Bloor, Pelkan and Allen;[13] the total phenol content of the blood, by the method of Theis and Benedict;[14] the chloride content of the urine, by the method of Volhard and Harvey,[15] and the bromide content of the blood (estimation), by the method of Wuth.[16]

Similarly, six dogs were placed in an oxygen chamber under normal living conditions, and a series of preliminary studies were made to develop a technic and to study the changes in the blood chemistry in the anoxic animal over long periods of time. The oxygen content of the inspired air was lowered to asphyxial levels, and in three cases death ensued.

In the cases of the dogs an explanatory note must be offered for the discrepancy between the percentage of oxygen in the inspired air and the percentage of oxygen desaturation of the arterial blood. This was due to the fact that in some instances, because of a few seconds of delay in the drawing of arterial blood, the dog took a few breaths of normal air. Three such breaths were found to be sufficient to raise the oxygen content of the arterial blood far above its previous level. In the case of J. K., there was a small percentage of desaturation of the blood, due to delay.

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PROTOCOLS

We feel that a protocol of each case is necessary to a complete understanding of the results obtained. However, limitations of space prevent inclusion of the results of each determination of the oxygen, carbon dioxide, temperature and humidity of the air in the chamber.

CASE 1.—J. A. was a single man aged 29. At the age of 10 years, while working on a farm, he had his first convulsion. He had two more attacks in the next two years. He was given phenobarbital and for two years had no attacks. For six or seven years prior to this study the attacks occurred at night, and in 1932 they averaged one per week. During 1934 he had only five attacks. There was no objective evidence of organic disease of the nervous system. No seizures occurred while he was in the chamber. However, he suddenly became extremely cyanotic and unconscious, with irregular respiration, periods of apnea and a rapid, thready pulse. Artificial respiration had to be resorted to. This occurred on his fourth day in the chamber, when the oxygen content of the air was 9 per cent.

CASE 2.—W. B., a man aged 35, had one child alive and well. At the age of 33, a week or two after an attack of influenza, he had a minor seizure. Seizures recurred frequently for a month. Then he had a severe sustained tonic convulsion which lasted two hours. At intervals after that he had at times warnings of attacks; attacks of short duration, with a sense of blurring and fogginess; attacks in which weakness of the right lower extremity developed, in which he sank down and got up immediately, and attacks of generalized convulsions. He became irritable, excitable and short tempered. He was operated on for suspected tumor of the brain in 1933, but none was found. After the operation he had attacks beginning with pallor of the face and staring, but no actual convulsions occurred. He had mild hemiparesis on the right. He had an "attack" while in the chamber when there was 14 per cent of oxygen in the inspired air.

CASE 3.—R. P., a man aged 28, had one normal child 16 months old. The patient contracted syphilis five years before the onset of seizures and received treatment. About six months afterward he had a convulsive seizure. About one and one-half years before the attack he sustained an injury in an automobile accident, being unconscious for a short time and dazed for a couple of hours. After the first attack he had recurrences once a month. Once they ceased for six months, and then for a period of two months he had one attack every week. The attacks began with an aura of "blankness," which was followed by a typical tonic-clonic seizure. There was no evidence of organic disease of the nervous system. No convulsion or attacks occurred during his stay in the chamber.

CASE 4.—J. K., a married man aged 46, suffered from grand mal attacks from August 1933 to April 1934 and after that had petit mal attacks. In the first attack he had blurring of vision, after which his head turned to the left, his right arm rose up and he turned to the left and fell unconscious. Subsequently he was weak and drowsy. The grand mal seizures ceased after bromide therapy, but he commenced to have petit mal attacks, in which he became mentally confused and speechless but remained conscious, each attack lasting a few seconds. He said that his memory was poorer. There was no objective evidence of disease of the nervous system. He had a questionable attack when in the chamber at an oxygen percentage of 9.

CASE 5.—J. R., a boy aged 16, was struck by an automobile when he was 7 years old and lost consciousness for thirty minutes. The skull was said to have

been fractured. With the exception of severe headache, there were no immediate symptoms of injury to the brain. One week later he experienced an attack of petit mal lasting a few minutes. Similar attacks occurred at intervals of several weeks. In the four years prior to this study grand mal attacks appeared at the same intervals. His last attack occurred three and a half weeks before hospitalization. He had an attack two days after admission to the hospital. After a short period of confusion his head and eyes turned to the left, and as his body began to turn to the left he lost consciousness and fell. Then a tonic-clonic convulsion ensued. Although no evidence of intracranial injury was found, the history of skull fracture and a focal character of the beginning of the attacks suggested the possibility of a local pathologic condition. He felt as though he were going to have an attack when the oxygen content of the chamber air was at 8.5 per cent. None, however, developed.

CASE 6.—R. R., a man aged 27, who had been married seven years, had one child alive and well. At the age of 19 years, while at work, the patient had an attack beginning with the seeing of bright spots before his eyes. After an interval sufficiently long to permit him to sit down, he lost consciousness. During this period his extremities were rigid, and on regaining consciousness he slept for three hours. For two years the attacks appeared every three or four weeks. During the following year he was free from any form of attack. In 1930 the attacks recurred from about every four to six weeks but caused no loss of consciousness. Only the right upper extremity became rigid, the fingers became fixed in a semiflexed clawlike position and the right side of the face twitched. At the time of this study each attack lasted about thirty seconds. No critical evidence of organic disease was found, but the focal character of the attacks pointed to some local pathologic condition. He had no attack while in the chamber.

CASE 7.—F. W. was a man aged 23. At the age of 15, one year after an attack of polyneuritis following the eating of strawberries and immediately after the drinking of two glasses of wine, he slumped in his chair as though asleep. He remained in this condition for an hour and then awakened but continued to feel drowsy. One year later he suddenly fell, losing consciousness. He began to drink alcoholic beverages, and the attacks occurred once a week, then as often as three or four times a day. He was placed under treatment and had no attacks from January 1935 to the time of his entrance into the hospital on March 4. The attacks occurring prior to January were often ushered in with a feeling of puckering of the lips and at times a sense of a peculiar odor. There ensued a sudden loss of consciousness lasting five minutes, during which he would lie in a "limp" state. In addition to these attacks, for about one and a half years he had attacks of automatism, occurring several times a week, until January 1935, after which he had one or two a week. In an attack which occurred in the hospital he wandered to another patient's bed, took a footstool with him, sat on it and started to undress. When spoken to, he regained full consciousness. A significant fact was his statement that he could bring on an attack frequently by playing a trombone. There was no objective evidence of organic disease of the nervous system. He had an attack while in the chamber when the oxygen content of the inspired air was 14 per cent.

CASE 8.—E. O., a man aged 36, had one child living and well. During the first year after his marriage, eleven years previously, he had a nocturnal attack. Similar attacks continued to occur about once a week for seven or eight years. After 1930 the attacks occurred in series of three or four a day and then none for three or four weeks. During the month prior to hospitalization he had two

attacks, and while being examined in the hospital he had an attack. He suddenly stopped following directions, lost consciousness, pursed his lips, became cyanotic, had tonic spasms, made pushing movements with the arm and turned the head to the right. After a few minutes he sat up and searched feverishly for some object, uttered a few nonsensical phrases, half climbed out of bed and continued to pluck at the bedclothes and bedsprings; fifteen minutes later he became normal. In another attack he fell over limply on the table, arose and walked about for a few minutes as if in search of something. There were no objective signs of organic disease of the nervous system. He had no attack while in the chamber.

Case 9.—A. H., a man aged 39, was married but had no children. He had gonorrhea fifteen years previously. The first seizure, eight to nine years before, occurred when he was in bed. He "wanted to get out and go to work very bad." He did not know what happened. The spells were the same for the next two years, coming on in the night two or three times a year. Four or five years later he had an attack during the day. After that the attacks occurred every two to four weeks, but he did go as long as six months without one. Two or three years before this study was made he began to have an aura, which lasted for a few seconds and consisted of a feeling of faintness and a feeling as if his "eyes were going out"; then everything would turn black. It took him from fifteen to thirty minutes to recover. His last attack occurred eighteen months before entry. There was no evidence of organic disease of the nervous system. He left the chamber at his own request after twenty-four hours because he felt unwell. There were no seizures.

Case 10.—A. O., a single man aged 18, had an attack while in Sunday school at 6 years of age. He felt weak, faint and dizzy and on going to the fountain for a drink fell limply and was unconscious for two minutes. There were no tonic or clonic movements. Nine years later he had a similar attack at 7 a. m. For a space of a minute or two he had an aura of dizziness and weakness, followed by unconsciousness. He partially regained consciousness and tried to get up, but everything "went black" and he fell back again. He thought he was unconscious for four or five minutes. After that he had no more than three similar attacks. There was no evidence of organic disease of the nervous system. He complained of cramps in the legs after being in the chamber for twelve hours and requested release. He had no seizures while there.

Case 11.—P. D., a married man aged 29, had been an alcoholic addict since the age of 12 years. In 1931 while driving a car he "passed out," finding himself sitting in his place a short time afterward. These attacks occurred two or three times a week. During the following year psychic equivalents of seizures developed, during which he was destructive and maniacal. The attacks increased in frequency to one or two a day. Starting in 1933 the attacks began with an aura of déjà vu, followed by loss of consciousness and a convulsive seizure. In 1933 he had an acute alcoholic psychosis, from which he recovered. There was no objective evidence of organic disease of the nervous system. He was thought to have a psychopathic personality and a convulsive disorder. He had a number of attacks during the period of hospitalization. He had a fugue when in the oxygen chamber, the percentage of oxygen being 15.

Case 12.—D. B., a woman aged 33, had one child. At the age of 14 years the patient began to have attacks with turning of the head to the left and then loss of consciousness and tonic-clonic convulsions, followed by vomiting and sleep. They occurred several times a month until she was 25 but diminished in frequency after pregnancy. During a period of three years, while taking 1.5 grains (0.97 Gm.)

of phenobarbital a day, she had no attacks. Lately, after the attacks had recurred, she thought she was able to prevent the loss of consciousness and generalized convulsions by grasping her head when it began to turn at the beginning of an attack. There was no objective evidence of organic disease of the nervous system.

The condition in this case ordinarily would be classified as idiopathic epilepsy, but attention should be paid to the focal nature of the beginning of the attack. During the period of hospitalization she was given 1.5 grains (0.97 Gm.) of phenobarbital daily. No attacks occurred while she was in the chamber.

TABLE 1.—*Acid-Base Equilibrium of the Plasma (Arterial Blood) of Anoxic Dogs*

Dog	Date	Oxygen Content of Chamber, %	Oxygen Content, Vol. %	Oxygen Capacity, Vol. %	Desaturation, Vol. %	Hematocrit, Reading, Vol. %	Total Phenol, Mg. per 100 Cc.	Chloride, Mg. per 100 Cc.	Carbon Dioxide, Vol. %	Inorganic Sulfur, Mg. per 100 Cc.	Inorganic Phosphorus, Mg. per 100 Cc.	Protein, Mg. per 100 Cc.
1	2/26*	21.00	.....	.....	.....	....	2.16	600	40.0	1.66	3.40	6.51
	2/26*	7.00	17.56	19.02	7.70	....	2.32	564	50.4	1.66	3.30	6.80
	2/26*	5.75	15.76	19.12	17.60	....	2.76	576	37.2	0.64	4.60	6.51
2	3/15*	21.00	14.44	19.85	27.30†	48.0	3.00	544	51.3	1.42	2.65	7.20
	3/18*	6.00	17.21	22.08	22.10	51.0	3.70	604	14.5	....	5.10	7.81
	3/19*	6.00	14.90	20.15	26.00	46.3	3.45	580	22.1	5.90	....	5.68
3	4/12	21.00	20.20	21.66	6.70	44.6	2.40	520	53.2	1.43	3.14	6.42
	4/15	21.00	20.31	22.17	8.40	45.0	1.70	500	44.7	1.78	2.90	7.00
	4/16*	21.00	20.20	20.35	0.70	39.5	1.79	552	33.4	1.51	2.95	6.51
	4/18*	6.00	16.74	20.74	19.30	62.4	....	536	23.0	3.74	....	7.20
	4/19*	5.00	21.05	25.05	16.00	50.0	4.16	520	32.4	2.40	2.46	7.81
	4/19*‡	3.00	20.31	23.90	10.80	51.0	3.05	508	24.0	2.67	2.28	7.44
4	5/28	21.00	18.51	18.93	2.20	40.5	....	556	43.9	3.50	3.10	5.51
	5/31*	21.00	16.43	18.87	7.60	46.0	....	512	41.7	....	2.60	6.05
	6/ 6*	5.00	8.16	19.96	59.10	43.0	....	536	28.7	2.94	2.20	6.70
	6/ 6*	5.00	8.16	19.52	58.20	39.0	....	536	30.5	3.08	2.50	6.51
5	4/ 1	21.00	21.14	21.18	0.20	44.7	1.71	510	49.4	1.58	2.83	6.73
	4/ 2	21.00	20.98	21.00	1.00	45.0	1.76	528	48.5	1.63	2.80	5.86
	4/ 4*	21.00	17.37	17.39	0.10	42.0	2.48	542	50.4	3.70	3.58	6.11
	4/ 6*‡	7.00	.....	.....	.....	44.0	1.20	588	28.7	5.60	1.70	7.16
6	3/ 6*	21.00	.....	.....	.....	....	....	500	36.2	....	....	....
	3/ 7*	7.00	21.19	23.92	11.41	52.5	2.52	476	32.4	....	2.63	7.33
	3/ 7*	8.50	.....	.....	.....	....	....	390	....	....	....	....
	3/ 8*	8.00	18.51	.....	.....	39.5	2.78	492	37.2	....	....	9.02
	3/ 8*	8.50	.....	.....	.....	....	....	464	33.8	....	....	....
	3/ 9*	6.00	17.11	22.30	22.33	42.7	4.65	568	28.7	1.60	3.36	8.28
	3/11*	6.00	17.68	20.84	15.16	45.7	2.90	564	23.0	1.90	5.90	7.81
	3/12*‡	5.50	12.13	20.90	42.00	45.3	4.10	576	19.2	0.92	4.95	8.21

* Day spent in the oxygen chamber.
† Venous blood.
‡ Death occurred.

CASE 13.—E. W., a married woman aged 41, had had attacks without an aura every two weeks since the onset of menstruation. The spells had become less frequent, the last ones having occurred five months and one month, respectively, before this study was made. Physical examination revealed no evidence of organic disease of the nervous system, and the patient experienced no attack while in the chamber.

RESULTS

We studied the symptomatology in these cases while the oxygen content of the inspired air was gradually lowered. The respiration was labored before the patient became cyanotic, the cyanosis appearing usually at a concentration of 14 per cent of oxygen in the inspired

TABLE 2.—*Acid-Base Equilibrium of Plasma (Arterial Blood) and Intake and Output of Chloride, Phosphorus and Sulfur of Human Beings During Anoxia*

Case	Date	Oxygen Content of Chamber, %	Oxygen Content, Vol. %	Oxygen Capacity, Vol. %	Desaturation, Vol. %	Hematocrit Reading, Vol. %	Total Phenol, Mg. per 100 Cc.	Total Halide, Mg. per 100 Cc.	Inorganic Sulfur, Mg. per 100 Cc.	Inorganic Phosphorus, Mg. per 100 Cc.	Plasma Protein, Gm. per 100 Cc.	Bromide, Mg. per 100 Cc.	Cholesterol, Mg. per 100 Cc.	Carbon Dioxide, Vol. %	24 Hour Period: Output: Chloride, Gm. per 100 Cc.	Output: Inorganic Sulfur, Gm. per 100 Cc.	Output: Inorganic Phosphorus, Gm. per 100 Cc.	Output: Vol., Cc.	24 Hour Period: Intake: Chloride, Gm. per 100 Cc.	Intake: Total Sulfur, Gm. per 100 Cc.	Intake: Total Phosphorus, Gm. per 100 Cc.	Intake: Vol., Cc.
J. A.	10/18	.....	.....	.....	.....	....	....	...	....	....	....	...	...	....	9.07	0.18	0.66	5,340	6.10	0.75	1.16	2,350
	10/19	.....	.....	.....	.....	....	....	...	....	....	....	...	...	....	6.29	0.40	0.54	3,700	....	....	....	6,400
	10/20	.....	.....	.....	.....	....	....	...	....	....	....	...	...	....	6.18	0.25	0.69	5,625	....	....	....	3,200
	10/21*	21.00	.....	.....	.....	....	....	460	0.63	4.10	7.10	200	162	61.0	5.35	0.15	0.57	3,080	....	....	....	2,500
	10/22*	.....	.....	.....	.....	....	....	...	....	....	....	...	...	....	2.76	0.15	0.39	2,940	....	....	....	2,600
	10/23*	11.50	.....	.....	.....	....	....	464	1.03	3.10	6.60	...	125	52.0	5.66	0.17	0.33	2,980	....	....	....	2,000
	10/24*	9.50	.....	.....	.....	....	....	445	0.93	2.15	7.28	...	122	57.0	4.60	0.33	0.08	2,450	....	....	....	3,200
	10/25	21.00	.....	.....	.....	....	....	...	....	....	....	...	...	....	2.74	0.33	0.62	3,070	....	....	....	3,200
	10/26	.....	.....	.....	.....	....	....	...	....	....	....	...	...	....	6.56	0.22	1.06	2,735	....	....	....	2,080
	10/27	.....	.....	.....	.....	....	....	...	....	....	....	...	...	....	2.86	0.29	0.77	2,310	....	....	....	3,600
	10/28	.....	.....	.....	.....	....	....	...	....	....	....	...	...	....	1.02	0.44	0.45	3,000	....	....	....	3,200
W. B.	7/ 9	.....	.....	.....	.....	....	....	...	....	....	....	...	...	....	10.90	0.73	0.55	540	5.05	0.76	1.15	1,165
	7/10	.....	.....	.....	.....	....	....	...	....	....	....	...	...	....	5.60	....	0.48	578	....	....	....	600
	7/11*	21.00	.....	.....	.....	42.4	....	490	0.98	3.15	6.90	225	169	50.4	9.90	0.32	0.39	1,560	....	....	....	900
	7/12*	7.00	11.45	21.35	46.40	51.1	....	460	1.07	1.08	9.30	...	170	43.6	3.50	0.60	0.59	700	....	....	....	900
R. P.	7/ 9	.....	.....	.....	.....	....	....	...	....	....	....	...	...	....	9.00	0.83	0.89	2,210	5.05	0.76	1.15	2,400
	7/11*	21.00	22.19	22.29	.....	51.0	....	480	1.53	3.40	7.50	†	183	55.1	24.00	0.30	0.67	3,125	....	....	....	2,200
	7/12*	7.00	.....	.....	.....	50.0	....	450	1.18	4.60	8.90	...	192	48.5	....	....	....	.....	....	....	....	.....
J. K.	4/18*	21.00	.....	19.58	.....	44.0	1.68	460	3.20	2.40	7.05	100	...	57.5	....	....	....	.....	....	....	....	.....
	4/19*	9.00	18.63	19.87	6.20	44.8	1.38	440	5.10	2.99	6.95	...	...	49.4	....	....	....	.....	....	....	....	.....
J. R.	4/18*	21.00	.....	19.58	.....	45.0	1.56	450	3.00	3.65	7.80	†	...	61.7	....	....	....	.....	....	....	....	.....
	4/19*	8.50	11.58	20.73	44.10	46.5	1.39	420	4.70	2.15	7.50	...	...	54.0	....	...	....	.....	No special diet			
R. R.	4/ 8*	21.00	13.48	13.90	3.20	42.0	1.97	480	0.25	3.20	9.00	†	...	49.5	....	....	....	.....	....	....	....	.....
	4/ 9*	10.00	17.56	20.62	14.84	49.0	1.92	650	0.65	2.50	6.80	...	...	40.7	....	....	....	.....	....	....	....	.....
F. W.	4/ 8*	21.00	15.37	.....	.....	43.0	1.70	440	0.36	3.45	6.09	175	...	51.1	....	....	....	.....	....	....	....	.....
	4/ 9*	13-14	17.35	18.80	7.71	47.4	2.20	490	....	2.30	6.90	...	...	39.5	....	....	....	.....	....	....	....	.....
	4/ 9*	9.50	11.84	14.14	16.27	54.0	2.40	590	0.45	2.00	8.84	...	...	46.8	....	....	....	.....	....	....	....	.....
E. O.	7/29	.....	.....	.....	.....	....	....	...	....	....	....	...	...	....	8.40	0.90	0.93	1,900	5.05	1.14	1.72	2,100
	7/30*	21.00	20.10	20.20	.....	45.4	....	...	....	.....	8.90	†	...	48.6	6.10	0.91	0.97	1,750	....	....	....	2,000
	7/31*	8.50	10.10	20.20	50.00	47.0	....	460	....	1.96	8.10	...	...	41.2	8.10	0.91	0.89	1,100	....	....	....	2,200
	8/ 1	.....	.....	.....	.....	....	....	...	....	....	....	...	...	....	3.30	0.90	0.85	1,800	....	....	....	2,000
A. H.	7/29	21.00	.....	.....	.....	45.0	....	450	....	2.60	8.30	†	...	59.9	9.30	0.86	0.70	1,530	5.00	1.14	1.72	2,100
	7/30*	.....	.....	.....	.....	....	....	...	....	....	....	...	...	....	3.90	0.37	0.34	2,500	....	....	....	2,000
	7/31*	.....	.....	.....	.....	....	....	...	....	....	....	...	...	....	8.60	0.64	0.75	1,700	....	....	....	1,300
	8/ 1	.....	.....	.....	.....	....	....	...	....	....	....	...	...	....	1.40	0.56	0.59	1,900	....	....	....	1,700
A. O.	7/16	21.00	.....	.....	.....	47.0	....	480	1.71	3.35	7.80	†	...	....	6.00	0.38	0.55	1,045	5.05	0.76	1.15	1,400
	7/17	.....	.....	.....	.....	....	....	...	....	....	....	...	...	....	7.60	0.62	0.75	1,950	....	....	....	1,400
	7/18*	.....	.....	.....	.....	....	....	...	....	....	....	...	...	....	6.50	0.64	0.84	1,200	....	....	....	1,200
	7/19*	.....	.....	.....	.....	....	....	...	....	....	....	...	...	....				Incomplete				
P. D.	7/16	.....	.....	.....	.....	....	....	...	....	....	....	...	...	....	8.40	0.53	0.64	1,485	5.05	0.76	1.15	1,600
	7/17	.....	.....	.....	.....	....	....	...	....	....	....	...	...	....	3.00	0.39	0.59	1,470	....	....	....	1,600
	7/18*	21.00	.....	.....	.....	42.0	....	520	1.51	3.60	9.00	†	...	61.5	5.00	0.90	0.76	1,050	....	....	....	1,400
	7/19*	10.00	.....	.....	.....	49.0	....	450	2.01	2.07	9.60	...	...	57.5	4.20	0.89	0.64	1,200	....	....	....	700
E. W.	3/21*	21.00	.....	.....	.....	....	....	...	....	3.90	....	...	...	50.8	....	....	....	.....	....	....	....	.....
	3/22*	13.50	.....	16.28	.....	....	2.88	415	2.30	3.00	2.88	...	...	42.9	....	....	....	.....	....	....	....	.....
D. B.	3/21*	.....	.....	.....	.....	....	....	...	....	4.20	....	...	...	46.6	....	....	....	.....	No special diet			
	3/22*	13.00	.....	15.97	.....	....	3.45	420	4.70	2.55	3.45	...	...	39.0	....	....	....	.....	....	....	....	.....

* Day spent in oxygen chamber.
† The bromide content of the blood was less than 75 mg. per hundred cubic centimeters.

air, although in two cases cyanosis was not apparent until a level of 12 per cent of oxygen was reached. Usually, at the level of 14 per cent of oxygen in the inspired air the patient was extremely dyspneic on exertion. He would feel little troubled, but when the oxygen tension was lowered still further, to a level of 9 per cent of oxygen in the inspired air, he invariably became deeply cyanotic, dyspneic and confused. This, we felt, was the critical level below which it would be hazardous to go; for patient J. A., for instance, artificial respiration had to be used. In some cases irregular breathing was apparent at a level of 12 per cent of oxygen in the inspired air. It can be seen that the symptomatology differed in no wise from that seen in normal adults.[17]

Not one typical epileptic convulsion was produced in any patient. However, in all cases motor phenomena were observed at oxygen levels corresponding to the asphyxial stage. In one patient a seizure occurred when he was breathing air containing 13 or 14 per cent of oxygen. Two other patients felt as if they were going to have a seizure when the percentage of oxygen had been lowered to 9 and 8.5, respectively, and two other patients exhibited epileptic-like phenomena when there was 15 and 14 per cent of oxygen, respectively, in the respired air. These findings will be described in detail.

The seizure experienced by F. W. while in the chamber occurred at an oxygen level of 13 or 14 per cent. Another patient who was in the chamber at the time gave an eyewitness account. "W. was resting at the edge of his bed, without any guard, when he rose from his pillow and fell to the floor, striking his head first. He quivered a lot for about five minutes, his eyes staring toward the left. He was almost purple." After the seizure F. W. had a severe headache, which lasted about five hours. The noticeable feature of the blood chemistry at the time of the fit was the marked fall in the level of the carbon dioxide content. His roommate, R. R., under identical conditions, had no symptoms. When the oxygen content of the inspired air was lowered still further, F. W. had no seizures, and the carbon dioxide content of the blood rose, as did the chloride content. It seems, then, that he did not adjust well to anoxia. If the fit had been due to anoxia alone, then when the oxygen was lowered further he should have gone into a status epilepticus. An interesting fact is that he was the patient who by playing a trombone could bring on a seizure, which presumably was due to hyperventilation of short duration.

17. Schneider, E. C.: Physiological Effects of Altitude, Physiol. Rev. **1**:631-659, 1921. Douglas, C. G.; Haldane, J. S.; Henderson, Y., and Schneider, E. C.: Physiological Observations Made on Pike's Peak, Colorado, with Special Reference to Adaptation to Low Barometric Pressures, Phil. Tr. Roy. Soc., London, s.B **203**:185-318, 1912. Haldane.[3a] Barcroft.[3b]

J. K., at an oxygen percentage of 9 in the inspired air, felt as if he were going to have a seizure. "I felt my mouth twitching, my nerves shaking. I could see and hear, but I could not talk, as you know when you asked me questions. I felt weak and went into a cold sweat; you had hold of my right arm and so prevented the fit, as this is the one that goes up when I have a fit." To the observer he appeared to be unconscious. He was extremely cyanotic, and his respirations were hissing, deep, labored and irregular. His teeth were clinched, and his whole body twitched, but there were no clonic or tonic spasms, nor was there involuntary micturition or defecation. The eyes were deviated upward. The radial pulse was barely palpable. He did not complain when a needle was inserted into an artery, but he did when he was recovering. Presumably he was unconscious in the earlier period. The symptoms—a barely palpable radial pulse, muscle twitchings and low oxygen tension—point to a state of asphyxial acidosis rather than to an epileptiform seizure. When the blood was being drawn, some air entered the syringe, thus ruining the specimen for study. However, in this study the oxygen content of J. R.'s blood may be used, as it was an absolute control.

J. R. was under the same conditions as J. K., just mentioned. He felt as if he were going to have an attack when the oxygen content of the inspired air was 8.5 per cent. He presented symptoms identical with those of J. K.

Another patient observed that W. B. had an attack lasting from fifteen to twenty seconds when the oxygen content of the inspired air was 14 per cent. W. B. was staring straight ahead, and his left hand and leg twitched several times.

P. D., while in the chamber at a level of 15 per cent oxygen in the inspired air, made several short attempts to tear off the handle of the door, working at it for about five minutes. He remembered nothing of it afterward. Fourteen hours after removal from the oxygen room he had an attack of confusion, combativeness and loss of memory for that period. In the chamber he was garrulous, but after a while he seemed to settle down. Ordinarily he was a friendly person.

Thus, while they were in the oxygen chamber under the influence of moderate anoxia and therefore of alkalosis for a period of thirty hours, there were produced in patients with epilepsy three epileptiform equivalents. Two patients thought they were going to have an attack when a state of severe anoxia had been reached. This occurred after a stay in the chamber of thirty-six hours.

On reference to the table it will be seen that the changes in the blood chemistry recorded during anoxia, both mild and severe, of patients

with epilepsy did not differ essentially from those seen in dogs and from those reported in the literature. Considering the control determinations of the blood chemistry of these patients, we can see no disturbances of the acid-base balance. The total halide content of the blood during mild anoxia varied little in all the experiments, any change being noted in the nature of a lowering. At the same time the total protein content of the serum either remained stationary or showed a rise. Coincident with this the inorganic sulfate content of the blood almost invariably increased, while the phosphate content decreased. This was especially marked in dog 2, in which the inorganic phosphate level of the blood fell to nil and the sulfate content rose to 5.9 mg. per hundred cubic centimeters. In the case of dog 6, in which anoxia was prolonged for seven days, a fall of the phosphate level to nil was noted on the fourth day, with a subsequent rise to 4.95 mg. per hundred cubic centimeters. At the same time the sulfate level had fallen to 0.92 mg. per hundred cubic centimeters. Peters and his associates [4] observed a similar reduction in the phosphate content during anoxia, which they said was inexplicable as well as unexpected. Koehler and his associates,[18] in reference to the acidosis during severe anoxia, stated that it might be due in large part to a disturbance in the phosphate system, as has been claimed by Bourne and Stehle.[19] In two instances (R. R. and F. W.) when a more marked fall in the bicarbonate content of the plasma was noted, the total halide content increased markedly. This is in accordance with the findings of Peters and his colleagues.[4] However, in the case of the dogs, even though the bicarbonate content was lowered enormously, down to 14.5 volumes per hundred cubic centimeters, the total chloride content of the blood showed little change and often a lowering. In these cases it is to be noted that the total protein, inorganic sulfate and total phenol contents all showed a rise, whereas the inorganic phosphate level fell. Why the total chloride level should fall we cannot see. It might be suggested that a reaction to anoxia which is prolonged over the course of days differs from that produced more acutely, or it may be that the amount of nonvolatile acids produced was sufficient to compensate for the loss of bicarbonate.

The bicarbonate content of the plasma was not decreased markedly until the asphyxial levels were reached, this being especially well seen in dog 6, for which a level of 19.2 volumes of carbon dioxide per hundred cubic centimeters was obtained. This is in accordance with

18. Koehler, A. E.; Brunquist, E. H., and Loevenhart, A. S.: The Production of Acidosis by Anoxemia, J. Biol. Chem. **64**:313-323, 1925.

19. Bourne, Wesley, and Stehle, R. L.: The Excretion of Phosphoric Acid During Anesthesia, J. A. M. A. **83**:117-118 (July 12) 1924.

the findings of Henderson and Radloff,[20] as is the fact that only at this point did the total phenol content of the body show a marked rise. We are at present investigating this work in the light of the results obtained by Henderson and Radloff.

We are at a loss to explain the rise in the inorganic sulfate content of the blood and the fall in the inorganic phosphate content, which were usually, but not invariably, seen. It may be that these changes are part of the process whereby the sensitivity of the respiratory center is increased to its specific stimulus (Peters and his associates [4] and Koehler and his associates [18]).

No significant change can be seen in the twenty-four hour output of chloride, sulfate and phosphate of the five patients so examined. The calcium and the magnesium content of the diet were low, so that most of the phosphate was excreted in the urine.

In summary, then, we can say that the acid-base balance of patients with epilepsy in the interval between attacks appears to be normal—that they react as one would expect to anoxia, either mild or severe.

The absence of elevation of the chloride content of the blood of dogs in which the bicarbonate content was tremendously reduced seems difficult to explain. The rise in the inorganic sulfate content of the blood and the fall in the organic phosphate content also were puzzling.

COMMENT

We have observed the results of prolonged anoxia in thirteen epileptic patients under what we consider ideal conditions. The patients lived in rooms and were able to walk about and converse with their neighbors. The air breathed was under absolute control as to humidity, temperature and oxygen content. The oxygen content of the inspired air was reduced gradually over the course of thirty-six hours in the case of twelve patients. During the first thirty hours the average oxygen content of the air was 13.5 per cent, and in the subsequent six hours it was lowered to a level which was thought safe for the particular patient, i. e., from 7 to 9 per cent. The preliminary gradual induction of anoxia was used to prevent the undesirable effects of "mountain sickness." The oxygen content of the air breathed by the patient who stayed in for four days was given earlier in this paper.

In no instance did we observe a typical epileptiform seizure. One patient who was breathing an atmosphere containing 13 or 14 per cent of oxygen had an attack the significance of which has been discussed. Two other patients felt as if they were going to have seizures when

20. Henderson, Y., and Radloff, E. M.: The Chemical Control of Breathing as Shown in the Acid-Base Balance of the Blood, Under Progressive Decrease of Oxygen, Am. J. Physiol. **101**:647-661, 1932.

they breathed air containing 8.5 or 9 per cent oxygen, but, as has been shown, they were both suffering from severe anoxia. Two other patients exhibited epileptic phenomena when the oxygen content was 14 and 15 per cent, respectively. Motor phenomena were observed in every case when the oxygen content of the air was lowered to asphyxial levels. It should be noted that the patient who had a seizure and two others who felt as though they were about to have seizures were all subject to both petit mal and grand mal attacks. However, P. D., although also suffering from major and minor attacks, did not have a seizure.

To satisfy ourselves that the presence of excess bromide in the blood of these patients (they were all under bromide therapy up to a few days before the tests were carried out) was not a factor in the suppression of seizures, the bromide content of the blood was estimated for every patient when he entered the chamber. In only two cases was the bromide level sufficiently high to have prevented spontaneous convulsions. In the remainder it was so low that it could not be detected by the Wuth method.

The previous work on this subject has been carried out as an acute experiment lasting for minutes, with variable results. The patients have been subjected to a procedure which could not help but fill them with apprehension; and instead of the production of a state of uncomplicated anoxia, these patients have in all probability been reduced to an asphyxial condition. It is not to be wondered that great difficulty has been encountered in distinguishing between the symptoms manifested and true epileptic seizures. We have also noted the occurrence of loss of consciousness, intense cyanosis, rapid pulse rate and motor phenomena at these low levels. In the milder but definite grades of anoxia and therefore of alkalosis we have produced three epileptic phenomena only one of which (the fugue) we were inclined to regard as at all definite.

The reaction of these patients to anoxia, as judged by the symptomatology and acid-base balance, was the same as one would expect and in no way differed from that of normal persons or of control dogs.

We feel that the effect of anoxia per se on epileptic subjects under ideal conditions is not a factor in the production of seizures.

SUMMARY

Thirteen epileptic patients have been observed with regard to the effects of prolonged anoxia.

Five epileptic-like phenomena were obtained; we regarded only one as being a definite seizure and one as questionable.

Every patient exhibited excitation phenomena during severe anoxia.

The symptoms and acid-base balance of these patients during anoxia differed in no wise from those observed for dogs and normal human beings.

The acid-base balance of the patient with epilepsy in the interparoxysmal periods appears to be normal.

Anoxia per se does not seem to be a factor in the production of epileptic seizures.

Dr. Lewis J. Pollock and other members of the staff of the neurologic clinic assisted in the selection, control and observation of the patients from the neurologic standpoint.

Mr. W. W. Davison helped in the management of the oxygen chamber, and Mrs. B. Van Dyke and Miss S. Hart carried out the analysis of the blood.

CONGENITAL DEFECTS OF THE PERICARDIUM

HAMILTON SOUTHWORTH, M.D.
AND
CHARLES SUMMERS STEVENSON, M.D.
BALTIMORE

Congenital deficiency of the pericardial sac has never been correctly diagnosed during life. It is an anomaly which has aroused the attention largely of anatomists and embryologists. But in spite of its rarity we believe it is not without clinical significance.

The first case reported of absence of the pericardium was that of Realdo Colombo in 1559, but it seems probable in the light of present knowledge that this was merely a case of adherent pericardium. The first indubitable example of the condition was that reported by Baillie in 1793. Since then about fifty other cases have been described, but in many instances the protocols have been scanty and in none has the clinical side of the picture been stressed. The unusualness of the condition is further emphasized by the fact that in 1909 Versé found only two examples in thirteen thousand necropsy reports and that the case we are about to describe is the first in the series of over fourteen thousand cases in which autopsy was performed at the Johns Hopkins Hospital. The following case is reported because it is the first one in which an adequate clinical description has been available. The literature on the subject is subsequently reviewed.

REPORT OF A CASE

B. McD., a 46 year old Negress, was admitted to the medical service of the Johns Hopkins Hospital on March 23, 1936, and died in eight hours. Her critical condition precluded elaborate questioning, but apparently her health had been excellent save for a transient febrile illness with thoracic pain six years before her admission to the hospital. There were no complaints referable to the heart, and though she was not specifically questioned on this point, her family was unaware that she had any cardiac abnormality. Six days before entry she became ill, showing a typical onset of lobar pneumonia, with shaking chill, pain in the right side of the chest and bloody sputum. As her temperature fell, however, the pain radiated around to the precordium, and her physician sent her to the hospital because she was looking worse.

When the patient was admitted the temperature was 101 F. (rectal), the pulse rate 130, the respiratory rate 44 and the blood pressure 140 systolic and 70 diastolic.

From the Department of Medicine and the Department of Pathology, Johns Hopkins Hospital and University.

Physical examination showed a well developed Negress who was critically ill. Respirations were rapid and labored, with audible moisture. Slight cyanosis and definite jaundice were noted. She had a cough productive of tenacious, bile-stained sputum. Her psyche was clear, but she was apathetic. Dehydration was marked. The trachea was in the midline, but the heart seemed greatly displaced to the left, with a forcible apex impulse in the posterior portion of the axilla and no extension of dulness to the right of the sternum. The heart sounds were of fair quality, but there was a loud to and fro friction rub along the left margin of the heart, which, though affected by respiration, seemed predominantly cardiac in origin. Signs of consolidation were noted over the lower lobe of the right lung, being most pronounced in the interscapular region, with evidence of resolution below. There were no signs to suggest effusion into the pleura. At the base of the left lung scattered râles were heard, and laterally a pleural friction rub and slight dulness were noted. The abdomen was moderately distended, and the liver was felt 2 cm. below the costal margin. The veins of the neck were engorged.

A blood count showed 34,320 leukocytes, with 98 per cent neutrophils. The urine showed albumin (2 +) and a few leukocytes. The sputum contained 98 per cent type I pneumococci, and blood culture showed one hundred and twenty-four colonies of the same organism per cubic centimeter. The Wassermann reaction of the blood was 4+. Because of the extraordinary position of the heart a fluoroscopic study was made of the patient in bed. The heart was observed to be greatly displaced to the left and little, if any, enlarged. The pulsations were well seen. A shadow at the base of the right lung suggested pneumonia, but the costophrenic angle was clear. There was nothing indicative of fluid save a tiny layer in the interlobar fissure. The lower portion of the left lung was obscured by the heart, but no evidence of consolidation was discovered.

In spite of the use of type I pneumococcus antiserum, an oxygen tent, digitalis and sedatives, the course was rapidly downhill, and the patient died after eight hours. The clinical diagnosis was lobar pneumonia, bacteremia and pericarditis due to Pneumococcus type I, cardiac insufficiency and syphilis. The cardiac displacement remained unexplained, as there seemed to be neither a significant collection of fluid in the right pleura nor massive collapse of the left lung.

Autopsy.—The patient died on March 24, and autopsy was performed in four hours.

Gross Examination: The body weighed 54 Kg. and was 158 cm. long. The nutritional state was average.

The abdominal organs showed the usual arrangement, without peritoneal or diaphragmatic anomaly. The spleen was small, and the kidneys bore a few old scars. There was moderate sclerosis of the aorta.

As the anterior mediastinal connection with the sternum was cut from below upward in the routine removal of the sternum, it was discovered that this connection was absent above the level of the third costochondral junction and did not begin again for a distance of about 6 cm., thus forming a window of about that diameter connecting the two pleural cavities (fig. 1). Part of the upper lobe of the right lung protruded through the window and was adherent to the upper lobe of the left lung. The heart, covered with fresh fibrinous exudate, lay in the lower half of the left pleural cavity. No layer of pericardium separated it from the anterior wall of the chest, the left lung or the diaphragm. At the apex an old fibrous band, 1 cm. in diameter, bound it to the lateral thoracic wall, and the

epicardium was also adherent to the lower lobe of the left lung and to the left dome of the diaphragm. The left pleural cavity contained about 500 cc. and the right about 200 cc. of thin purulent fluid. The pleural surfaces of both lungs were covered with fresh fibrinous exudate. The two lobes of the left lung occupied the upper half of the left pleural cavity, while the heart lay below them.

Fig. 1.—Postmortem appearance of the relationship of the heart and the pleural cavities.

With the heart lying in the left pleural cavity, nothing was seen that even suggested a remnant of the left half of the parietal pericardium. A mass of fatty tissue formed the lower part of the anterior mediastinum below the interpleural window. The surface of this mass adjacent to the right auricle extended upward to form a partially encircling collar about the base of the heart and

beyond this merged with the left parietal pleura. The heart was not enlarged, and the great vessels showed their usual arrangement. The lateral displacement of the heart had caused no buckling of the aorta or pulmonary vessels. The myocardial walls were of usual thickness and normal appearance. All the valves were thin and delicate. There was slight sclerosis of the coronary arteries.

The upper lobe of the left lung was displaced upward and backward but contained air. The lower lobe, where it was fastened by fresh exudate to the heart, was collapsed but not consolidated. There was uniform gray consolidation of the lower lobe of the right lung. The upper lobe of the right lung contained air; the middle lobe was small and compressed but not consolidated. The lymph nodes at the hilus of the right lung and in the mediastinum above and below the interpleural window were enlarged. Two adenomatous nodules of the right lobe of the thyroid gland lay beneath the manubrium. The course of the two phrenic nerves was along the spinal column just posterior to the base of the heart; they were not involved in the abnormality.

Microscopic Examination: Confluent lobular pneumonia of the lower lobe of the right lung and patchy atelectasis of the lower lobe of the left lung were noted. The pleural surfaces of both lungs and of the epicardium showed a thick layer of exudate containing polymorphonuclear leukocytes. The exudate over the right lung gave evidence of early organization. The adhesive band at the apex of the heart consisted of scar tissue. Sections through the mass in the lower portion of the anterior mediastinum showed ordinary adipose tissue and a few small islands of lymphocytes. The myocardium was normal; sections through the surface revealed epicardium covered with exudate but no evidence of adherent parietal pericardium. There were subintimal thickenings and hyaline patches in the aorta and in the coronary arteries. Sections from the kidneys showed a few healed cortical scars and extensive vacuolation of the epithelial cells. The thyroid nodules were typical adenomas. There were senile changes in the genital organs and chronic inflammation of the urethra.

Culture.—Type I pneumococci were grown from the heart blood.

Pathologic Diagnosis.—The pathologic diagnosis was as follows: congenital defect of the pericardial sac, with the heart lying free in the left pleural cavity; connection of both pleural cavities through the anterior mediastinum; confluent lobular pneumonia in the lower lobe of the right lung; bilateral fibrinous pleurisy with adhesions; fibrinous epicarditis, with adhesions of the heart to the lower lobe of the left lung, to the left side of the diaphragm and to the lateral thoracic wall; scars of the kidneys, with vacuolation of the epithelium; arteriosclerosis and coronary sclerosis; thyroid adenomas; senility of the fallopian tubes and ovaries, and chronic urethritis.

Comment.—Since there was no pericardial sac enclosing the heart, but a common pleuropericardial cavity on the left, it could be said that there was no pericardium and that the heart was entirely surrounded by pleura. However, it seemed more logical, since there was a layer of mediastinum separating the heart from the right pleural cavity, that this represented the right leaf of the parietal pericardium and that it was the absence of only the left leaf of the parietal pericardium that released the heart into the left pleura. Death was the result of the over-

whelming pneumococcic infection, which in the absence of the usual pleural and pericardial barriers spread so as to produce extensive pleuropericarditis as well as bacteremia.

EMBRYOLOGY

The development of the human pericardium is a complex process the successive steps of which can be briefly summarized as follows: The intra-embryonic celomic cavity first appears as an empty sinus in the mesodermal segment at about the second somite stage (fig. 2 *III*). It is an extension into the embryonic mesoderm from the large extra-embryonic celom (fig. 2 *I* and *II*), which is found first in the human embryo in the third week. The intra-embryonic celom enlarges and is made up of the large pericardial celom and the two lateral pleuroperitoneal canals (fig. 2 *VI*). The latter connect at their lower ends with the extra-embryonic celom.

The ventral wall of the still-paired pericardial celom thickens to form the primordial epimyocardium (fig. 2 *IV*). The foregut then buds off from the yolk sac, and the two pericardial celomic cavities fuse; the two endocardial primordia likewise fuse into the one unpaired vessel (fig. 2 *V*) which later becomes the heart.

By the fourth week the septum transversum has begun to grow in from the ventral wall (fig. 2 *VII*), and it extends dorsally in the midline until it meets the gut. However, it leaves on each side a pleural canal through which the pericardial and peritoneal cavities communicate (fig. 2 *VII*). Each canal lies just medial to the common cardinal vein. The lungs begin to bud from the pulmonary ridge (fig. 2 *VIII*) and grow into the canal (fig. 2 *IX*). Two folds now begin to grow out from the common cardinal vein (ducts of Cuvier) on each side, the ventral fold being the pleuropericardial membrane and the dorsal fold being the pleuroperitoneal membrane (fig. 2 *IX*). When these membranes reach the medial wall of the pleuroperitoneal canal on each side of the lung bud, they fuse with it and thus wall off the pericardial and pleural cavities separately from the peritoneal cavity (fig. 2 *X*).

Three elements go to make up the diaphragm: the septum transversum, an ingrowth from the body wall and, lastly, the pleuroperitoneal membrane. Any deficiencies in the diaphragm result from the failure of this membrane to close completely over the original opening. Any deficiencies in the pericardial sac are due to the failure of the pleuropericardial membrane to close completely on one or both sides.

Two theories have been advanced in the attempt to explain why the pericardial defect is generally on the left. The first, advanced by Perna and by Plaut, is based on a developmental defect in vascularization. With the formation of the left innominate vein and the azygos

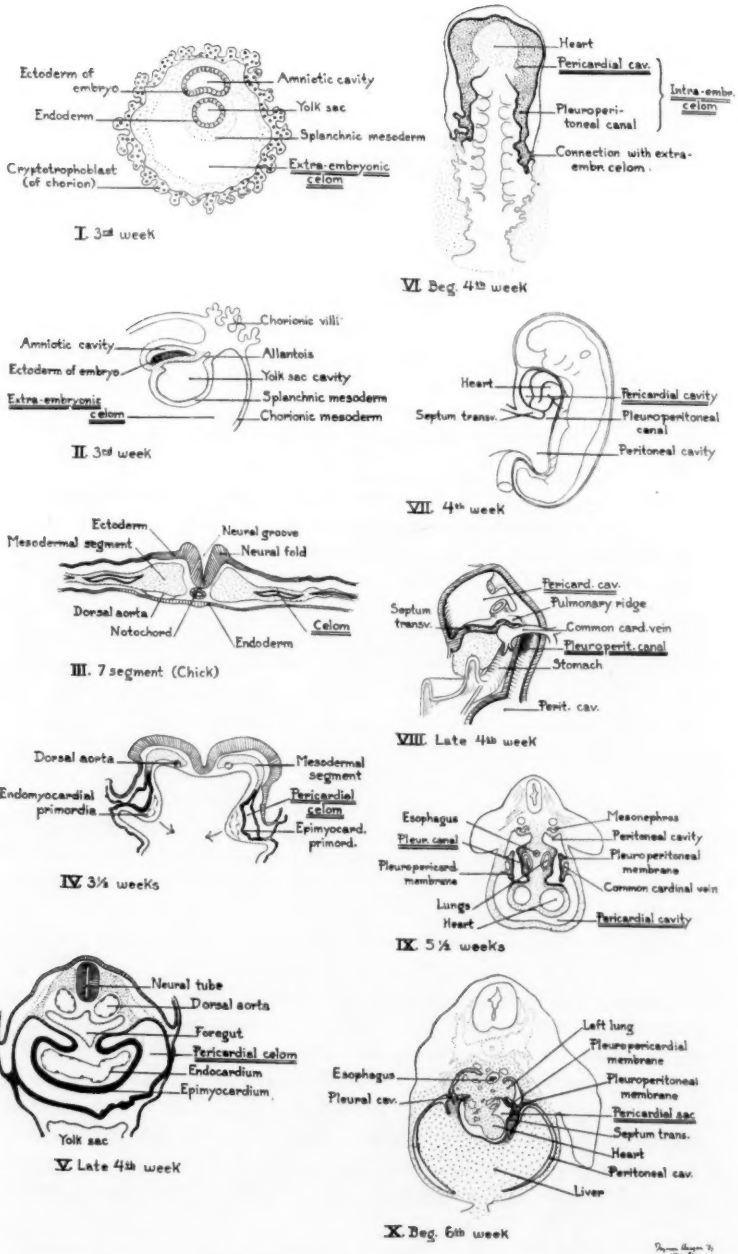

Fig. 2.—Development of the human pericardium (diagrams after Arey).

system in the eighth week of fetal life, the left common cardinal vein tends to atrophy and in the adult is represented by only the coronary sinus (Arey). The right common cardinal vein, however, finally develops into the superior vena cava. If, then, the atrophy of the left common cardinal vein were a little premature, incomplete development of the associated pleuropericardial membrane might result from a deficient blood supply. The second theory, advocated by Risel and by McGarry, is based on a primary disturbance in the development of the celomic cavities. McGarry suggested that the defect is generally on the left because the asymmetry of the liver and its rotation during the course of development put the greater tension on the left pulmonary ridge. Moore tends to favor the former of these two theories, because of the comparative rarity of other associated celomic anomalies.

ANALYSIS OF REPORTED CASES

In 1925 Moore was able to find references in the literature to sixty-four cases of pericardial defect, and subsequent authors have accepted his enumeration. According to this count our case would be the seventy-first. Moore, however, was able to locate only forty-two protocols, a number extended by Grant in 1926 to forty-six. We have looked up the references of these authors, tracing them back to their sources, and by adding the reports of cases published in the last ten years have been able to locate a total of fifty-four reports of cases. The cases of Realdo Colombo, Tulpio, Littré, Peyer, Lancisi, Brunner and Hoyer have been excluded, as in all probability they were instances of adherent pericardium, as originally stated by Perna. No case was found to be reported in the articles by Greenhow and by Parlavecchio, and the protocols by Ménière and by Breschet obviously refer to the same patient. Descriptions by Ferraresi, Weber, Verbeck, Henkel, Wittcke, Phoebus and Shugeninoff could not be traced. Examples of ectopia cordis and pericardial diverticulum have been omitted purposely.

The fifty-four cases thus on record are listed in the accompanying table. Two of them, those of Lawson Tait and Lebec, have been grouped as doubtful because of inadequate or atypical descriptions, a judgment concurred in by Perna. Seven other cases were those of fetuses or new-born infants so disfigured by anomalies as to be classified separately as monsters.[1]

1. Mönckeberg's second and third cases have not been so listed because, although one case was that of a new-born infant and the other was that of a 3 week old infant, the cause of death was not given in either case and the failure to describe other anomalies is presumptive evidence that none were present.

I. Definite Cases

No.	Author	Date	Sex	Age	Cause of Death	Cardiac Symptoms and Signs	Size of Heart Post Mortem	Type of Pericardial Defect	Pneumonitis	Pleurisy	Adhesions of Heart	Other Anomalies or Conditions
1	Baillie	1793	M	?40	.....	0	Very large	Common cavity on left	0	0	0	.....
2	Walter	1805	M	30	.....	.....	.....	Common cavity on left	.....	.....	.....	.....
3	Otto	1824	M	Adult	.....	.....	.....	Common cavity on left	.....	.....	.....	.....
4	Ménière (Breschet)	1826	M	28	Dysentery with perforation	0	Normal	Common cavity on left	0	0	To left lung and diaphragm	.....
5	Wolf	1827	F	42	Typhus	Angina, mild	Enlarged	Common cavity on left	.....	.....	.....	Pregnancy
6	Curling	1839	M	46	Ascending paralysis	0	Enlarged	Common cavity on left	.....	0	To lower lobe of left lung	.....
7	Baly	1850	M	32	Tuberculosis of lungs and peritoneum	0	Normal	Common cavity on left	Tuberculosis	Fresh exudate and adhesion to left lung		.....
8	Bristowe	1855	M	28	Pneumonia	.....	Enlarged	Common cavity on left	Pneumonia	¾ pint (350 cc.) of exudate	Old ones to upper lobe of left lung	Jaundice
9	Powell	1868	M	..	Tuberculosis of lungs and spontaneous pneumothorax	.....	.....	Foramen on left, small	Tuberculosis	Turbid fluid and air in pericardium	0	.....
10	Peacock	1866	M	75	Aortic valvular disease	.....	.....	Common cavity on left	.....	.....	To left lung	.....
11	Weisbach	1868	M	22	Pleuropericardial exudate	0	Enlarged, bifid	Foramen on left, large, with heart protruding	.....	Purulent pleuropericardial exudate	.....	Bifid heart
12	Björnström	1872	F	40	Colitis; gastric ulcer	0	.....	Common cavity on left	.....	.....	To upper lobe of left lung	.....
13	Faber	1878	M	51	Acute pleurisy	.....	.....	Common cavity on left	.....	Serofibrinous exudate all over heart and left lung		.....
14	Chiari	1880	M	46	Cirrhosis; tuberculous peritonitis	Only accentuated pulmonic second sound	Normal	Common cavity on left	.....	.....	.....	Deep fissure, upper lobes of both lungs

15	Chiari	1880	F	62	.....	0	Enlarged	Common cavity on left	.....	.....	To left lung	.....
16	Chiari	1880	M	60	Pleuropericarditis	.....	Enlarged	Common cavity on left	.....	Pleuropericarditis		.....
17	Pisek	1883	M	"Young"	Pneumonia	0	.....	Common cavity on left	Lobular pneumonia	Fresh patches	To left lung	.....
18	Hughes	1886	M	33	Advanced tuberculosis of lungs	No distinctive symptoms; cardiac dulness from right border of sternum for 2.5 inches (6.5 cm.) to left	Normal	Common cavity on left	Tuberculosis	.....	To left lung and diaphragm	.....
19	Adsersen	1887	M	25	Ruptured spleen; bronchopneumonia	.....	.....	Large foramen on left	Broncho-pneumonia	Serosanguineous effusion	.....	.....
20	Orth	1887	..	..	Rupture of aneurysm	.....	.....	Foramen on left	.....	Hemothorax and hemopericardium		Aneurysm ruptured into pericardium
21	Boxall	1887	F	28	Herniation of heart through defect	Symptoms of pulmonary embolism	.....	Foramen on left, large; heart protruding	.....	0	.....	3 days post partum
22	Schindewolf	1900	..	50	Volvulus, with postoperative death; old mitral endocarditis	Point of maximal impulse 3 fingerbreadths outside nipple	Very large	Common cavity on left	0	.....	.....	.....
23	Primrose	1901	M	50-60	Fever; abdominal pain	.....	.....	Foramen on left	0	.....	To parietal pericardium	Only 1 kidney
24	Saxer	1902	M	..	Tuberculous meningitis and peritonitis; old tuberculosis of lung	.....	.....	Common cavity on left	0	0	At apex	Pregnancy; death soon after delivery
25	Picchi	1907	M	60	Pneumonia and pleurisy	.....	Slightly enlarged	Common cavity on left	Pneumonia	Fibrinous pleurisy	To left lung	.....
26	Picchi	1907	F	31	Pneumonia	.....	.....	Common cavity on left	Pneumonia	0	.....	.....
27	Versé	1909	F	30	Cyanide poisoning	.....	Normal	Common cavity on left	0	0	To left lung	.....

Pericardial Defects—Continued

No.	Author	Date	Sex	Age	Cause of Death	Cardiac Symptoms and Signs	Size of Heart Post Mortem	Type of Pericardial Defect	Pneumonitis	Pleurisy	Adhesions of Heart	Other Anomalies or Conditions
28	Perna	1909	M	68	Chronic enteritis	0	Normal	Common cavity on left	0	0	To left lung	.....
29	Ebstein	1910	F	..	Cyanide poisoning	Palpitation after typhoid, but normal physical findings	.....	Common cavity on left	.....	.....	To left lung	.....
30	Schmincke	1912	M	30	Sepsis	0	.....	Foramen on left	.....	.....	.....	.....
31	Plaut	1913	M	30	Sepsis	0	Normal	Common cavity on left	0	0	To left lung and wall of chest	.....
32	Plaut	1913	M	18	Pyogenic meningitis	.....	.....	Common cavity on left	0	0	To left lung and wall of chest	.....
33	Cameron	1913	M	67	Bronchopneumonia; emphysema; chronic nephritis	.....	Enlarged	Common cavity on left	Bronchopneumonia	0	0	? Traumatic defect
34	McGarry	1914	M	65	Dementia and gastritis	0	.....	Foramen on left, large	.....	.....	0	Several peritoneal anomalies
35	Chase	1916	M	Adult	Tuberculosis of lungs	.....	Normal	Common cavity on left	Tuberculosis	.....	0	Kyphoscoliosis
36	Lang	1921	M	..	Colitis; hydrothorax; ascites	0	Normal	Common cavity on left	0	Shaggy epicarditis	To left lung	.....
37	Canavan	1924	..	56	Dementia paralytica	.....	Very large	Common cavity on left	0	0	0	.....
38	Mönckeberg	1924	M	39	.....	.....	.....	Foramen on left	.....	.....	On all sides	.....
39	Mönckeberg	1924	M	3 wk.	.....	.....	.....	Common cavity on left	.....	.....	To left lung	.....
40	Mönckeberg	1924	M	Newborn	.....	.....	.....	Common cavity on left	.....	.....	To left lung	.....
41	Grant	1926	M	52	Carcinoma of esophagus; pneumonia	.....	.....	Foramen on left, large; heart protruding	Bronchopneumonia	.....	To left lung, delicate	.....

42	Beck	1931	M	56	Pneumonia; cardiac insufficiency; arteriosclerosis; hypertension	Cardiac insufficiency	Enlarged	Common cavity on left	Lobular pneumonia	1,200 cc. of clear fluid	Right auricle to pericardial leaf	.....
43	Watt	1931	M	52	Coronary occlusion	Coronary occlusion	Enlarged	Common cavity on left	.....	.....	0	Long heart with bifid apex
44	Chiodin	1932	F	64	Carcinoma of cervix; postoperative death	Normal heart by physical examination	.....	Foramen on left, large; ? smaller one on right	.....	.....	To left lung and pericardial rudiment	.....
45	Barsoum	1935	M	35	Cardiac insufficiency	? Adherent pericarditis	Greatly enlarged	Common cavity on left	.....	.....	0	.....
							II. Doubtful Cases					
46	Tait	1869	F	29	Atheromatous mitral stenosis	Dyspnea and anemia; signs of mitral stenosis	.....	No pericardium, left or right	.....	.....	.....	.....
47	Lebec	1874	..	..	.....	.....	.....	Common cavity on left	.....	.....	.....	Only 2 aortic cusps
							III. Cases in Monsters					
48	Meckel	1826	M	Fetus	Gross malformation	.....	.....	Foramen on left, small	.....	.....	.....	.....
49	Keith	1907	..	Fetus	Gross malformation	.....	.....	Foramen on left	.....	.....	.....	Defect in diaphragm
50	Keith	1907	..	Full term fetus	Anencephaly	.....	.....	Foramen on left; left auricle protruding	.....	.....	.....	Anomalies of central nervous system
51	Risel	1912	F	Newborn	Gross malformation	.....	.....	Foramen on left; smaller one on right	.....	.....	.....	Anomalies of central nervous system, abdomen and lungs
52	Risel	1912	F	Fetus	Gross malformation	.....	.....	Common cavity on left	.....	.....	.....	Defects of central nervous system and in left side of diaphragm
53	Risel	1912	M	Newborn	Gross malformation	.....	.....	Foramen on left	.....	.....	.....	Anomalies of central nervous system and other anomalies
54	Egbert and Little	1935	..	18 hr.	Multiple abnormalities	? Dextrocardia	.....	Common cavity on left	.....	.....	.....	No dextrocardia; anomalies largely on right

Analyzing the data regarding the forty-six cases obtained by including our own case and excluding the two doubtful ones and the seven monsters, we find that with one possible exception (Chiodin's [2] case) the defect was present only on the left side. Among the seven cases in monsters there was one (Egbert and Little) in which the defect was entirely on the right, and there was one (Risel's first case) in which the defect, like that in Chiodin's case, was thought to be bilateral. Lawson Tait's case, in which no vestige of pericardium was found anywhere, is open to suspicion, both because the description is meager and because the heart, though said to be lying free between the lungs, had no serous surface.

It therefore appears that the defect in nearly every instance is on the left. The type of defect varies from a small foramen connecting the pericardial and the left pleural cavity to one in which there is virtual absence of the left leaf of the parietal pericardium, leaving the heart and the left lung together in a common pleuropericardial cavity.

Moore classified his forty-two cases under three categories: (1) those in which the heart and the lung occupied a common serous cavity (59.5 per cent of the cases), (2) those in which there was only a foramen between the pericardial and the pleural sac (21.4 per cent) and (3) those in which there was either no trace of pericardium or only rudiments thereof (19.1 per cent). It is our feeling that Moore's third type of condition, the existence of which he himself admitted was dubious, was represented entirely by doubtful cases and that the condition has never been conclusively demonstrated. As between the first and the second category we find, as Moore did, about three times as many cases in the former as in the latter. In thirty-four (or 76 per cent) of our forty-six basic cases there was a common serous cavity on the left for both the heart and the left lung, while in eleven (or 24 per cent) there was only a foramen on the left and the heart remained in the pericardial sac. In six cases plus, of course, the seven cases in monsters, there were other congenital anomalies, in addition to the defect of the pericardium. Two affected the heart, one the lungs, one a pleural cavity, one a kidney and one the peritoneum. Since in a number of instances only the heart was carefully described, it may well be that other defects were overlooked.

Thirty-three of our basic cases (77 per cent) occurred in males, as against ten in females. This is in agreement with the finding of Maude Abbott, who listed seventeen males and six females. The age at the time of death varied from birth to 75 years, with a mean of 41.6 years. In comparison, the mean age at death for the United States area of

2. Chiodin was frank enough to admit that the smaller defect present on the right may have been an artefact produced at autopsy.

registration for 1900 was 35.1 years.[3] The discrepancy between these figures is probably due to the fact that in our series only 5.3 per cent of the cases represent infant mortality, while in the census report deaths of infants under 1 year of age made up 20.8 per cent of the total. If, therefore, deaths of infants under 1 year of age are excluded from both series, the mean age at death in our series of cases of pericardial defects becomes 43.9 years, while that for the registration area becomes 44.2 years.

These figures indicate that the anomaly has no appreciable influence on life expectancy. In only one instance (Boxall) was death apparently due directly to the defect. The case was that of a woman of 28 who three days post partum died suddenly, with symptoms suggestive of pulmonary embolism. Autopsy disclosed that the whole heart had herniated through a large foramen in the left leaf of the pericardium and had become partially strangulated. It was suggested that changes in intrathoracic pressures following delivery were responsible for this mishap. In fifteen cases the absence of cardiac symptoms was commented on, while in only three were circulatory symptoms recorded that were not obviously due to associated disease, such as hypertension or coronary thrombosis. In two of these cases (those of Wolf and Ebstein) there was mild angina, and in one case the symptoms occurred after typhoid. In the third case it was believed during life that there was adherent pericarditis; death was due to cardiac insufficiency the cause of which was not explained.

In twenty-three instances the size of the heart was described. In four of the fourteen hearts said to be enlarged the enlargement was presumably due to associated cardiovascular diseases (coronary sclerosis, hypertension, chronic nephritis and mitral endocarditis). This leaves nineteen cases; in nine cases the heart was of normal size, which agrees with the observations of Grant that in only 50 per cent of the cases was the heart enlarged.

Although it thus appears that a pericardial defect is rarely the direct cause of death or of cardiac symptoms and that it does not necessarily cause cardiac enlargement, it may yet be detrimental to health by exposing the heart to pulmonary infection. This has been recognized previously by Abbott and by White, and the case cited is a conspicuous example. How serious a menace this may be is shown by the fact that in nine (19 per cent) of the cases listed in our series death was due to pneumonia while in twelve (27 per cent) there was fresh pleuropericarditis of some kind. In six instances (cases reported by Bristowe, Pisek, Adsersen, Picchi [case 1], Beck and ourselves)

3. Mortality Statistics, 1900-1904, Special Reports, United States Department of Commerce and Labor, Bureau of Census, 1906, p. 22.

pleuropericarditis was associated with pneumonia, while in three others (cases reported by Lang, Chiari [case 2] and Weisbach) its origin was not clear. In all nine, save perhaps in Adsersen's case, in which there was also a ruptured spleen, it was responsible for death. In two cases (those of Baly and Powell) pleuropericarditis was associated with pulmonary tuberculosis, and in Orth's case an aortic aneurysm produced a massive hemopericardiothorax by rupturing into the pericardium. Further evidence of former, albeit localized and transient, pleuropericardial infections is found in the fact that in twenty-five (74 per cent) of the thirty-four cases in which the serous surfaces were adequately described, there were adhesions between the epicardium and the left lung, the diaphragm or the pericardial remnant. In one instance (Perna) these adhesions were studied histologically and, as expected, showed evidence of old inflammation. It may be deduced that the presence of these adhesions shows that pleuropericardial infection is by no means always fatal; at least they indicate that it is common. No correlation could be made out between the size of the heart and the presence or absence of adhesions.

DIAGNOSIS

The clinical diagnosis of congenital defect of the pericardium has never been made during life. Maude Abbott has stated, however, that this need not be impossible and should be based on (1) the greatly increased mobility of the heart, (2) its occasional hypertrophy without clinical cause and (3) its frequent displacement to the left. In our patient the mobility was not adequately tested, owing to the patient's extreme illness, and was probably impaired anyway by the adhesions and the plastic exudate, but the cardiac pulsations under the fluoroscope were conspicuous. Cardiac enlargement was not present, in spite of the presence of adhesions. The unexplained displacement of the heart to the left without deviation of the trachea was the source of much clinical comment. Thus our case bears out at least one of Abbott's diagnostic criteria. The hypothecation of these criteria is, of course, partly presumptive. Clinical data on increased cardiac mobility are entirely lacking, though the approximately 50 per cent incidence of cardiac enlargement is definite. The incidence of displacement is also rather uncertain. In the 24 per cent of cases in which there was only a pleuropericardial foramen on the left, the heart was in normal position. Of the 76 per cent of cases in which there was a common pleuropericardial cavity on the left, ours is the first in which an adequate antemortem description of the cardiac position has been given. For the others since the anatomic description was given only after the anterior thoracic wall had been removed and the left lung had been collapsed through the opening of the left pleura, the data were rather uncertain as to the

cardiac position. But it seems logical, as Maude Abbott has maintained, that the complete absence of the left leaf of the parietal pericardium should cause some luxation of the heart to the left. We therefore feel that, although the diagnosis is probably impossible in cases in which the defect is represented only by a foramen, in those in which there is a common cavity on the left the diagnosis may be suspected from (1) unexplained displacement of the heart to the left and further confirmed if, in the absence of adhesions, there is (2) abnormal mobility of the heart. Unexplained cardiac enlargement (3), if present, would be further evidence in favor of the diagnosis, though its absence would not be significant.

SUMMARY

A description is given of a patient showing congenital absence of the left leaf of the parietal pericardium, with an interpleural window in the upper portion of the anterior mediastinum.

This is the first case reported in the literature in which adequate clinical data have been given and in which fluoroscopic examination has been included.

In a survey of the literature forty-five definite instances of this defect have been found, together with seven other instances in monstrous births and two doubtful cases.

Analysis of these cases reveals that the defect was almost invariably on the left; that in 76 per cent of the cases it was so complete on that side that the heart and the left lung were in a common serous cavity; that in 77 per cent of the cases the subject was a male, and that the condition is not incompatible with normal life, having in only one instance been directly responsible for death and having otherwise possibly caused cardiac symptoms in only three cases.

Unexplained cardiac enlargement may occur (in about half the cases), but it is apparently not related to the presence or absence of adhesions.

The chief danger from the defect lies in exposing the heart to pulmonary infection, with death in 27 per cent of the cases, including our own, associated with pleuropericarditis.

Although in no case as yet has the condition been diagnosed ante mortem, this should be possible in some instances, on the basis of certain criteria adapted from Maude Abbott.

NOTE.—Since the writing of this article an interesting report has appeared by E. Dahl (Med. rev., Bergen **54:** 312 [July] 1937) of a man aged 28 with bilateral exudative pulmonary tuberculosis in whom pneumopericardium appeared and persisted after artificial pneumothorax was induced through the left axilla. The author stated the opinion that this was a case of congenital defect but could not prove it was not due to the disease or to trauma. The diagnostic interest is obvious.

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FOUR LEAD ELECTROCARDIOGRAM IN CASES OF RECENT CORONARY OCCLUSION

A. BOHNING, M.D.
AND
L. N. KATZ, M.D.
CHICAGO

The value of electrocardiograms in cases of recent coronary occlusion has been definitely established. The added value of records obtained from leads with one electrode placed on the chest has recently come into prominence. Sufficient information has been published [1] to establish a fair basis for their interpretation, and obscure points are rapidly being clarified.

Accumulated evidence has indicated that the chest lead is often of definite assistance in determining the presence, the location and to some degree the age of myocardial infarcts. The published reports of a number of cases in which autopsies were performed furnish additional evidence of the accuracy of these electrocardiographic interpre-

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From the Heart Station, Michael Reese Hospital.

Aided by the A. D. Nast Fund for Cardiac Study.

1. (*a*) Wolferth, C. C., and Wood, F. C.: Electrocardiographic Diagnosis of Coronary Occlusion by Use of Chest Leads, Am. J. M. Sc. **183**:30, 1932; (*b*) Further Observations upon the Use of Chest Leads in the Electrocardiographic Study of Coronary Occlusion, M. Clin. North America **16**:161, 1932. (*c*) Wood, F. C.; Bellet, S.; McMillan, T. M., and Wolferth, C. C.: Electrocardiographic Study of Coronary Occlusion: Further Observations on the Use of Chest Leads, Arch. Int. Med. **52**:752 (Nov.) 1933. (*d*) Wilson, F. N.; Macleod, A. G.; Barker, P. S.; Johnston, F. D., and Klosternmeyer, L. L.: The Electrocardiogram in Myocardial Infarction with Particular Reference to the Initial Deflections of the Ventricular Complex, Heart **16**:155, 1933. (*e*) Hoffman, A. M., and Delong, E.: Standardization of Chest Leads and Their Value in Coronary Thrombosis and Myocardial Disease, Arch. Int. Med. **51**:947 (June) 1933. (*f*) Levine, Louis: Chest Leads in Coronary Occlusion, M. J. & Rec. **136**:421, 1932. (*g*) Goldbloom, A. A.: Clinical Evaluation of Lead IV (Chest Leads), Am. J. M. Sc. **187**:489, 1934. (*h*) Bohning, A., and Katz, L. N.: The Four Lead Electrocardiogram in Coronary Sclerosis, ibid. **189**:833, 1935. (*i*) Katz, L. N., and Kissin, M.: A Study of Lead IV, Am. Heart J. **8**:595, 1933. (*j*) Liberson, A., and Liberson, F.: The Value of Posterior-Anterior Chest Leads in Cardiac Diagnosis, Ann. Int. Med. **6**:1315, 1933. (*k*) Master, Arthur M.: The Precordial Lead in One Hundred and Four Normal Adults, Am. Heart J. **9**:511, 1934. (*l*) Shipley, R. A., and and Halloran, W. R.: Four Lead Electrocardiogram in Two Hundred Normal Men and Women, ibid. **11**:325, 1936. (*m*) Roth, Irving R.: On the Use of Chest Leads in Clinical Electrocardiography, ibid. **10**:798, 1935.

tations, but the significance of some details is still in controversy. Thus, some authors have stressed the contour of the T wave;[2] others, the contour and direction of the QRS complex[3] and still others, the appearance of the deviation in the ST segment.[4] In the greater number of instances the abnormalities in the precordial leads are in accord with those in the conventional three leads, but this is not true of all cases. The reason for this has not as yet been clearly established. There are a number of instances in which the chest lead is characteristic of infarction, but the conventional leads show none of the classic changes.[5] In a smaller group the conventional three leads may show the characteristic type of change, but the chest lead may be atypical.[6] It is therefore not surprising that there is some feeling of uncertainty in regard to the interpretation of chest leads. In the hope that we might be able to clarify some of this confusion, we have made a careful study of the four lead electrocardiogram with a large group of patients.

PLAN OF THE STUDY

(*a*) *Selection of Cases.*—The records of 200 consecutive patients from the charity wards, private pavilion and clinics of Michael Reese Hospital were studied. These patients had been referred for electrocardiograms during years 1934, 1935 and 1936. The selection was made on the basis of abnormalities in four lead

2. Wood, F. C., and Wolferth, C. C.: Huge T-Waves in Precordial Leads in Cardiac Infarction, Am. Heart J. **9**:706, 1934.

3. (*a*) Johnston, F. D.; Hill, I. G. W., and Wilson, F. N.: The Form of the Electrocardiogram in Experimental Myocardial Infarction: II. The Early Effects Produced by Ligation of the Anterior Descending Branch of the Left Coronary Artery, Am. Heart J. **10**:889, 1935. (*b*) Wilson, F. N.; Hill, I. G. W., and Johnston, F. D.: The Form of the Electrocardiogram in Experimental Myocardial Infarction: III. The Later Effects Produced by Ligation of the Anterior Descending Branch of the Left Coronary Artery, ibid. **10**:903, 1935. (*c*) Wilson, F. N.; Johnston, F. D., and Hill, I. G. W.: The Form of the Electrocardiogram in Experimental Myocardial Infarction: IV. Additional Observations on the Later Effects Produced by Ligation of the Anterior Descending Branch of the Left Coronary Artery, ibid. **10**:1025, 1935. Wilson and others.[1d]

4. (*a*) Wood, F. C., and Wolferth, C. C.: An Electrocardiographic Study of Experimental Coronary Occlusion: The Inadequacy of the Three Conventional Leads in Recording Certain Characteristic Changes in Action Current, J. Clin. Investigation **11**:815, 1932. (*b*) Wolferth, C. C.; Wood, F. C., and Bellet, S.: Acute Cardiac Infarction Involving Anterior and Posterior Surfaces of the Left Ventricle: Electrocardiographic Characteristics, Arch. Int. Med. **56**:77 (July) 1935. (*c*) Wood, F. C., and Wolferth, C. C.: Experimental Coronary Occlusion, ibid. **51**:771 (May) 1933. (*d*) Bellet, S., and Johnston, C. G.: The Effect of Coronary Occlusion upon the Initial Phase of the Ventricular Complex in Precordial Leads, J. Clin. Investigation **13**:725, 1934.

5. Wolferth and Wood.[1a] Katz and Kissin.[11] Wood and Wolferth.[4a]

6. Wolferth and Wood.[1b] Katz and Kissin.[11]

electrocardiograms which were indicative of *recent* myocardial infarction. Cases in which no diagnostic electrocardiographic features were revealed in the initial or serial curves were rejected regardless of the clinical picture. Many of the records were obtained within a few hours after the clinical attack, and a second record was often obtained within from twenty-four to forty-eight hours. These were followed in many instances by curves obtained every three or four days during the first two weeks and then every week or every fortnight during the rest of the patient's stay in the hospital. After leaving the hospital many patients returned every few months for follow-up study.

TABLE 1.—*Sex and Age Incidence in Present Series of Two Hundred Cases of Myocardial Infarction*

	Total Cases, Percentage	Known Dead (68%), Percentage	Autopsies (25%), Percentage
Men	76	75.7	88
Women	24	24.3	12
Age at time of attack			
Under 30 years	0.5	0.0	0
30 to 39 years	5.0	4.5	0
40 to 49 years	21.0	15.0	20
50 to 59 years	38.5	30.5	28
60 to 69 years	29.5	42.5	44
70 to 79 years	5.0	6.0	4
80 years or more	0.5	1.5	4

TABLE 2.—*Incidence of Mortality in the Two Hundred Consecutive Cases of Coronary Occlusion*

	Type of Infarction			
	Anterior	Posterior	Combined	All Types
Total number of cases	119	73	8	200
Fate unknown, %	25.0	29.0	12.5	26.0
Known to be alive, %	38.0	48.0	25.0	41.0
Known to be dead, %	37.0	23.0	62.5	33.0
Died in hospital, %	25.0	15.0	50.0	22.5
Autopsy obtained, %	12.5*	2.5	37.5	10.0

* Two cases of coronary sclerosis without infarction.

Six hundred and fifty records were thus obtained. In 44 cases only one record was made, usually because death occurred before a second could be obtained. In the remaining 156 cases the average number of records was four, the least number being two and the greatest twenty. In 32 cases the curves covered only the first week of illness, and in 33 only the stay in the hospital; in the other 91 cases there were follow-up records. Autopsies were obtained in 20 of the 200 cases. In 5 other cases not in the original series autopsy was performed while this report was being prepared. Our report therefore includes 25 cases of proved recent myocardial infarction in which four lead electrocardiograms were made (table 3 and figs. 1 to 7, inclusive). For comparison we have added 2 cases of recent multiple small infarcts and 8 cases of moderately advanced coronary sclerosis without infarcts in all of which autopsy was performed (table 3 and figs. 8 to 10, inclusive).

(*b*) *Criteria Used in Analyzing the Records.*—The changes observed in our 25 cases in which autopsy was performed were correlated with the electrocardio-

TABLE 3.—*Summary of Pertinent Autopsy Data in Thirty-Five Cases**

	Chart	Sex	Age	Myocardial Involvement: Anterior: Anterior Infarction	Myocardial Involvement: Anterior: Apical Infarction	Myocardial Involvement: Posterior: Posterior Infarction	Myocardial Involvement: Posterior: Basal Infarction	Myocardial Involvement: Posterior: Septal Infarction	Myocardial Involvement: Depth of Injury: Fibrosis	Myocardial Involvement: Depth of Injury: Fatty Changes	Myocardial Involvement: Depth of Injury: Epicardial Involvement	Myocardial Involvement: Depth of Injury: Endocardial Involvement	Type of Coronary Involvement: Right: Circumflex Branch	Type of Coronary Involvement: Right: Posterior Branch	Type of Coronary Involvement: Left: Left Descending Branch	Type of Coronary Involvement: Left: Circumflex Branch	Associated Data: Condition of Arteries: Coronary Sclerosis	Associated Data: Condition of Arteries: Generalized Sclerosis	Associated Data: Condition of Arteries: Aortic Sclerosis	Associated Data: Condition of Arteries: Kidney Involvement: Glomeruli	Associated Data: Condition of Arteries: Kidney Involvement: Arterioles	Associated Data: Condition of Arteries: Kidney Involvement: Medium-Sized Arteries	Associated Data: Condition of Heart: Hypertrophy	Associated Data: Condition of Heart: Dilatation	Associated Data: Condition of Heart: Valvular Involvement	Associated Data: Condition of Heart: Pericarditis	Associated Data: Pulmonary Involvement: Pneumonia	Associated Data: Pulmonary Involvement: Pulmonary Embolism	Associated Data: Pulmonary Involvement: Pulmonary Infarction	Associated Data: Pulmonary Involvement: Cerebral Involvement	Diagnostic Leads: Leads I to III Alone	Diagnostic Leads: Lead IV Alone
Anterior infarction																																
With thrombosis	1 *A*	F	62	R	..	..	..	R	..	+	+	+	..	Th	Th	..	+	+	+	..	+	..	+	..	..	+	+	..	..	+	+	+
	1 *B*	M	42	R	..	..	..	..	+	+	+	+	..	..	Th	..	+	..	+	..	..	..	..	..	..	..	+	..	..	..	+	+
	1 *C*	M	42	Or	Or	..	..	Or	..	..	+	+	N,Pl	..	Th	Pl	+	+	+	..	..	..	+	..	..	+	+	..	..	..	+	+
	1 *D*	M	63	R	R	..	..	R	+	+	+	+	..	..	Th	Pl	+	+	+	..	+	..	+	..	Sc	+	+	..	..	..	+	+
	1 *E*	M	80	R	..	..	..	R	+	+	+	+	N,Pl	..	Th	Pl	+	+	+	..	+	..	+	..	Sc	..	+	..	..	..	0	+
	1 *F*	M	54	R	..	..	..	Old	..	..	+	+	..	..	Th	N,Pl	+	..	+	..	..	..	+	..	..	+	+	..	..	..	+	+
	1 *G*	M	50	R	..	..	..	R	+	..	+	+	Pl	..	Th	OPl	+	+	+	..	..	..	+	+	..	..	..	..	..	..	0	+
	1 *H*	M	67	R	R	..	..	..	+	+	..	+	Pl	Pl	Th	Pl	+	+	+	..	..	..	+	..	Sc	..	+	..	..	..	0	+
With occluding sclerotic plaques	2 *A*	M	75	R	..	..	..	..	+	..	+	..	N,Pl	..	OPl	..	+	+	+	+	+	..	+	..	..	..	..	+	+	..	+	+
	2 *B*	M	50	Old,R	An	..	..	..	..	..	+	+	N,Pl	..	OPl	..	+	+	+	+	..	+	..	+	Sc	+	..	..	..	..	0	+
	2 *C*	M	50	Old,R	..	..	..	R	..	..	+	+	OPl	..	OPl	N,Pl	+	+	+	+	..	+	+	+	Sc,Rh	..	..	..	..	+	0	+
	2 *D*	F	58	R	R	..	..	R	+	..	+	+	OPl	..	OPl	..	+	+	+	..	..	..	+	+	Sc	+	..	..	..	..	0	+
	3 *A*	M	45	Old	An	..	..	R	+	..	+	+	NOS	..	N,Pl	..	+	+	+	..	..	..	+	+	Rh	..	..	..	..	..	0	0
	3 *B*	M	60	Old,R	..	..	..	R	+	..	+	+	NOS	..	N,Pl	OPl	+	+	..	+	+	..	+	..	Sc	..	+	..	..	+	0	0
	3 *C*	M	62	R	R	..	..	Old	..	+	+	+	..	OPl	N,Pl	..	+	+	+	+	+	..	+	..	..	..	+	+	..	..	0	0
Posterior infarction																																
With thrombosis	4 *A*	M	65	..	..	An	R	An,Per	..	..	+	+	Th	..	OPl	Pl	+	+	..	+	..	..	+	..	..	+	..	..	..	+	+	+
	4 *B*	M	64	..	..	Old	Old	..	+	+	+	+	Th	..	Pl	..	+	+	+	..	..	..	+	+	Sc	..	+	..	..	..	+	+
	4 *C*	M	50	..	..	Old	Old	..	..	+	+	..	Th	..	Pl	..	+	+	+	..	..	..	+	+	..	..	+	..	..	..	+	+
With occluding sclerotic plaques	4 *D*	M	66	..	..	Old	..	Old	+	..	+	+	NOS	OPl N	CA	..	+	+	+	+	+	..	+	+	Sc	..	..	..	..	..	0	0
Combined anterior and posterior infarction																																
Without aneurysm	5	M	53	R	R	Old	Old	..	+	+	+	+	Th,Old	..	Th,R	N,Pl	+	+	..	..	..	..	+	..	Sc	..	..	..	..	..	+	+
	6 *A*	M	67	Old	..	R	R	R	..	+	+	+	Th	N,Pl	N,Pl	OPl	+	..	+	..	..	+	+	..	Sc	+	+	..	..	..	0	+
	6 *B*	M	65	Old	Or	Old	..	..	+	..	+	..	Th,Old	..	OPl	..	+	+	+	..	+	..	+	+	..	..	..	..	..	..	+	+
With aneurysm	7 *A*	M	48	An	An	An	..	An	..	..	+	+	N	N	Th	OPl	+	..	+	..	..	+	..	..	..	+	+	+	+	+	0	+
	7 *B*	M	43	An	An	Old	An	An,Or	+	..	+	+	OPl	OPl	Old Th	N,Pl	+	+	+	+	..	..	+	+	Sc	..	..	..	+	..	0	0
	7 *C*	F	60	Or	An	Old,R	..	An,Or	+	..	+	+	Th	N,Pl	Or OPl	OPl	+	+	+	+	..	+	+	+	Rh	..	..	..	..	..	+	0
Multiple small infarctions	8 *A*	F	49	..	..	..	..	..	+	..	+	+	Pl	Pl	Pl	Pl	+	+	+	+	+	..	+	+	Sc	..	+	+	..	..	0	0
	8 *B*	F	49	..	..	..	..	..	+	+	+	+	NOS	Pl	Pl	Pl	+	+	+	..	..	..	..	..	..	..	+	..	..	..	0	+
Coronary sclerosis without infarction																																
Indeterminate electrocardiographic type	9 *A*	M	44	..	..	..	..	..	+	+	+	..	Pl	..	Pl	..	+	+	+	+	+	+	+	+	Sc	..	..	..	..	..	0	+
	9 *B*	M	74	..	..	..	..	..	+	..	+	..	Pl	..	Pl	..	+	+	+	..	..	..	+	+	Rh	..	..	..	..	..	0	+
	9 *C*	M	68	..	..	..	..	..	+	+	+	..	..	..	N,Pl	N,Pl	+	+	+	+	+	..	+	+	Sc	+	+	+	..	..	0	+
	9 *D*	M	57	..	..	..	..	..	+	..	..	..	NOS	Pl	NOS	Pl	+	+	+	..	..	..	..	..	Sc	..	..	..	..	..	0	0
	9 *E*	M	79	..	..	..	..	F	+	+	+	..	..	..	Pl	..	+	+	+	+	..	+	+	..	Rh	..	+	..	..	..	0	+
Electrocardiogram resembling anterior infarction	10 *A*	M	55	..	..	..	..	..	+	..	..	..	Pl	..	Pl	..	+	+	+	+	+	+	+	+	Sc	..	+	..	..	..	+	+
	10 *B*	M	68	..	..	..	..	..	+	+	..	..	CA,Pl	..	OPl	..	+	+	+	+	..	+	+	..	Sc	..	+	..	..	..	+	+
	10 *C*	M	67	..	..	..	..	..	+	..	..	..	NOS	..	N,Pl	..	+	+	+	+	..	+	+	..	Sc	..	+	..	..	..	0	+

* An indicates aneurysm. R

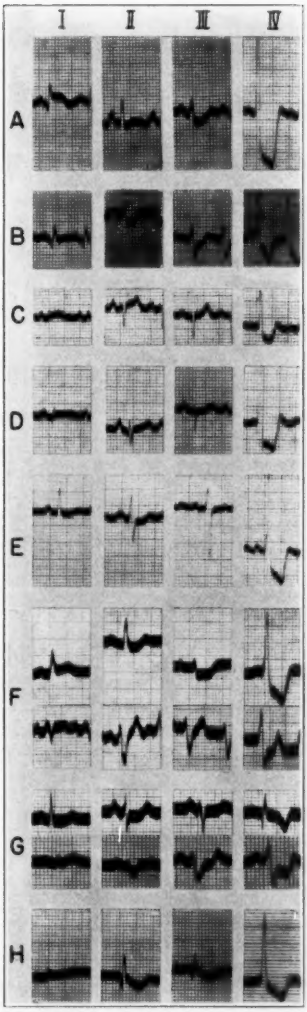

Fig. 1.—Electrocardiograms of 8 patients (cases A to H) with proved uncomplicated infarction of the anterior wall due to a suddenly occurring thrombus in the left anterior descending coronary artery. The necropsy reports are summarized in table 3.

Case A		Case B		Case C		Case D	
Attack.....	8/29/35	Attack.....	4/ 1/35	Attack.....	5/18/35	Attack.....	6/18/33
Curve taken.	8/30/35	Curve taken.	4/ 1/35	Curve taken.	5/23/35	Curve taken.	6/22/33
Death.....	8/31/35	Death.....	4/ 5/35	Death.....	6/10/35	Death.....	7/ 9/33
Case E		**Case F**		**Case G**		**Case H**	
Attack.....	5/20/35	Attack.....	2/24/35	Curve taken		Attack.....	12/16/32
Curve taken.	5/23/35	Curves taken	2/24/35	before attack	7/ 8/35	Curve taken.	12/16/32
Death.....	5/23/35		2/27/35	Attack.....	6/19/36	Death.....	12/22/32
		Death.....	2/27/35	Curve taken.	6/22/36		
				Death.....	6/24/36		

TABLE 4.—*Analysis of Abnormalities in Standard Three Leads*

	Types of Infarction											
	Anterior			Posterior			Combined			All Types		
	Series A Consecutive Cases	Series B Known Fatal Cases	Series C Autopsies	Series A Consecutive Cases	Series B Known Fatal Cases	Series C Autopsies	Series A Consecutive Cases	Series B Known Fatal Cases	Series C Autopsies	Series A Consecutive Cases	Series B Known Fatal Cases	Series C Autopsies
Number of cases in series	119	44	15	73	17	4	8	5	6	200	66	25
Percentage of cases in series	59.5	66.7	60.0	36.5	25.7	16.0	4.0	7.6	24.0	100.0	100.0	100.0
	Frequency of Abnormality, Percentage											
Changes in rhythm												
Extrasystoles	3.4	9.1	6.7	4.1	0.0	0.0	12.5	0.0	0.0	4.0	6.0	4.0
Auricular fibrillation	5.9	5.0	20.0	2.7	11.8	0.0	0.0	0.0	0.0	4.5	12.1	12.0
QRS deviations												
Intraventricular block	6.7	13.6	26.7	2.7	11.8	50.0	25.0	20.0	66.7	6.0	13.6	40.0
Low "voltage"	13.4	18.2	66.7	1.4	0.0	0.0	25.0	0.0	33.3	9.5	12.1	48.0
Slurring	99.2	100.0	100.0	98.6	100.0	100.0	100.0	100.0	100.0	99.0	100.0	100.0
Notching	37.8	45.5	33.3	41.1	52.9	25.0	100.0	100.0	66.7	41.5	51.5	40.0
Left axis shift	16.8	29.5	26.7	15.1	23.5	0.0	25.0	20.0	33.3	16.5	27.3	24.0
Left ventricular preponderance	22.7	25.0	33.3	50.7	47.0	25.0	25.0	40.0	33.3	33.0	31.8	32.0
Right axis shift	4.2	6.8	6.7	0.0	0.0	0.0	0.0	0.0	0.0	2.5	4.6	4.0
ST deviations												
Negative: ST_1	38.6	47.7	40.0	68.5	94.1	100.0	75.0	80.0	66.7	51.0	62.1	56.0
ST_2	47.6	61.4	66.7	39.7	17.6	50.0	25.0	20.0	33.3	45.5	46.9	56.0
ST_3	26.9	38.6	55.3	6.8	0.0	0.0	12.5	20.0	0.0	19.0	27.3	32.0
Positive: ST_1	16.8	25.0	40.0	5.5	0.0	0.0	0.0	0.0	0.0	12.0	16.6	24.0
ST_2	18.5	13.6	13.3	35.6	58.8	25.0	12.5	20.0	16.7	24.5	27.7	16.0
ST_3	25.2	15.9	20.0	63.0	88.2	100.0	75.0	60.0	33.3	41.0	37.8	36.0
T deviations												
Negative: T_1	63.9	65.9	33.3	1.4	0.0	0.0	25.0	40.0	50.0	39.5	46.9	32.0
T_2	37.0	27.3	13.3	49.3	64.7	50.0	62.5	60.0	33.3	42.5	39.3	24.0
T_3	9.2	18.2	13.3	78.1	82.3	100.0	37.5	20.0	50.0	35.5	34.8	36.0
Convex: ST_1	20.2	27.3	40.0	0.0	0.0	0.0	0.0	0.0	0.0	12.0	18.1	24.0
ST_2	0.8	2.3	0.0	11.0	17.6	0.0	0.0	0.0	0.0	4.5	6.0	0.0
ST_3	0.0	0.0	0.0	49.3	70.6	75.0	25.0	20.0	16.7	19.0	19.7	16.0
Diphasic: T_1	5.9	9.1	13.3	15.1	17.6	25.0	25.0	20.0	33.3	10.0	12.1	20.0
T_2	8.4	15.9	20.0	11.0	5.9	25.0	0.0	0.0	0.0	9.0	12.1	16.0
T_3	1.7	2.3	6.7	1.4	0.0	0.0	25.0	20.0	0.0	2.5	3.0	4.0
Iso-electric: T_1	2.5	4.5	0.0	1.4	0.0	0.0	0.0	0.0	0.0	2.0	3.0	0.0
T_2	5.9	9.1	0.0	0.0	0.0	0.0	12.5	0.0	16.7	4.0	6.0	4.0
T_3	4.2	2.3	0.0	4.1	0.0	0.0	12.5	20.0	0.0	4.5	3.0	0.0
Q deviations												
Q_1 present	43.7	36.4	40.0	37.0	23.5	0.0	37.5	20.0	33.3	41.0	31.8	32.0
Q_3 present	43.7	38.6	33.3	69.9	76.5	100.0	100.0	100.0	50.0	55.5	53.0	48.0
S deviations												
S_1 present	47.6	38.6	26.7	32.9	41.2	25.0	50.0	20.0	0.0	42.0	37.8	20.0
S_3 present	57.1	56.8	40.0	46.6	35.3	0.0	25.0	40.0	50.0	52.0	50.0	36.0
Q and S deviations												
Q_1 and S_3 present	27.7	25.0	26.7	23.3	5.9	0.0	0.0	0.0	0.0	25.0	18.1	16.0
Q_3 and S_1 present	25.2	25.0	13.3	23.3	35.3	0.0	37.5	20.0	0.0	25.0	27.3	8.0

TABLE 5.—*Analysis of Deviations in Lead IV*

		Types of Infarction											
		Anterior			Posterior			Combined			All Types		
		Series A Consecutive Cases	Series B Known Fatal Cases	Series C Autopsies	Series A Consecutive Cases	Series B Known Fatal Cases	Series C Autopsies	Series A Consecutive Cases	Series B Known Fatal Cases	Series C Autopsies	Series A Consecutive Cases	Series B Known Fatal Cases	Series C Autopsies
Number of cases in series		119	44	15	73	17	4	8	5	6	200	66	25
		Frequency of Abnormality, Percentage											
P_4	Positive	46.2	56.8	66.7	34.3	23.5	75.0	75.0	80.0	83.3	43.0	50.0	72.0
	Diphasic	16.8	18.2	13.3	20.6	29.4	0.0	25.0	20.0	0.0	18.5	21.2	8.0
	Iso-electric	21.9	22.7	20.0	15.0	23.6	0.0	0.0	0.0	0.0	18.5	21.2	12.0
	Negative	15.1	2.3	0.0	30.1	23.5	25.0	0.0	0.0	16.7	20.0	7.6	8.0
Q_4*	Absent	53.8	63.6	80.0	6.8	0.0	0.0	0.0	0.0	0.0	34.5	42.4	48.0
	Deep	11.8	9.0	0.0	80.8	76.4	75.0	50.0	40.0	16.6	38.5	28.8	16.0
QRS_4†	Monophasic upright	49.6	61.4	73.3	5.5	0.0	0.0	0.0	0.0	0.0	31.5	41.0	44.0
	Mainly positive	26.1	27.3	20.0	6.8	5.9	25.0	50.0	60.0	83.3	20.0	24.2	36.0
	Diphasic 1st phase down	19.3	9.0	6.7	72.6	88.2	75.0	50.0	40.0	16.7	40.0	31.8	20.0
	Diphasic 1st phase up	4.2	2.3	0.0	1.4	0.0	0.0	0.0	0.0	0.0	3.0	1.5	0.0
	Mainly down	0.8	0.0	0.0	13.7	5.9	0.0	0.0	0.0	0.0	5.5	1.5	0.0
ST_4	Positive	5.1	4.5	0.0	58.9	82.3	50.0	37.5	40.0	0.0	25.0	27.3	8.0
	Iso-electric	10.9	4.5	0.0	4.1	11.8	0.0	12.5	0.0	16.7	8.5	6.0	4.0
	Negative, —2 mm. or less	44.5	41.0	13.3	30.2	0.0	25.0	50.0	40.0	50.0	39.5	30.4	24.0
	Negative, more than —2 mm	39.5	50.0	86.7	6.8	5.9	25.0	0.0	20.0	33.3	26.0	36.3	64.0
T_4	Positive	43.7	25.0	6.7	4.1	5.9	0.0	25.0	20.0	0.0	28.5	19.7	4.0
	Diphasic	33.6	41.0	33.3	5.5	0.0	0.0	12.5	20.0	33.3	22.5	28.8	28.0
	Negative, less than —8 mm	18.5	25.0	53.3	63.0	41.1	75.0	62.5	60.0	33.4	36.0	31.8	52.0
	Negative, —8 mm. or more	4.2	9.0	6.7	27.4	53.0	25.0	0.0	0.0	33.3	13.0	19.7	16.0

* Primary negative deflection.
† Main deflection.

TABLE 6.—*Classification of Types of Coronary Insufficiency*

	Type of Myocardial Involvement		Type of Coronary Involvement	Location of Myocardial Involvement	Most Common Type of Electrocardiographic Change		Cases Illustrating the Type
I. Subacute	Definite myocardial infarction	A. Uncomplicated or classic forms	Thrombotic occlusion	Anterior infarction	ST_1 + T_1 −	QRS_4 + ST_4 − T_4 + or ±	8 cases (chart 1)
				Posterior infarction	ST_3 + T_3 −	QRS_4 ± ST_4 + T_4 − −	3 cases (charts 4*A* to *C*)
		B. Complicated or atypical forms	Sclerotic occlusion	Anterior infarction	ST_1 − T_1 −	QRS_4 + T_4 ±	7 cases (charts 2 and 3)
				Posterior infarction	T_3 −	QRS_4 + or ±	1 case (chart 4*D*)
			Both arteries occluded	Old posterior with recent anterior infarction	Often like anterior infarction		4 cases (charts 5, 7*A* and *B* and 11*A*)
				Old anterior with recent posterior infarction	Often like posterior infarction		4 cases (charts 6*A* and *B*, 7*C* and 11*B*)
			No complete occlusion	Multiple small infarcts	Atypical		2 cases (chart 8*A* and *B*)
II. Chronic, progressive or nonprogressive	Fibrosis without infarction		Advanced coronary sclerosis	No infarct visible; fibrosis usual	1. Like anterior infarction 2. Like posterior infarction 3. Indeterminate		2 cases (chart 10 *A* and *B*) 5 cases (chart 9)
III. Acute, transitory	Transitory ischemia		Indeterminate	Indeterminate	ST and T deviations variable		2 cases (charts 8*C* and 10*C*)

graphic changes in cases reported in the literature with autopsy data.[7] In this manner the electrocardiographic criteria for the following two groups were established: (1) recent anterior type of infarct, and (2) recent posterior type of infarct. These criteria are based, therefore, on the study of the electrocardiograms in a total of 239 cases in which the diagnosis was verified at autopsy. In the greater number of cases reported in the literature only the conventional three leads were recorded, but in our own cases and a limited number of the others four lead records were made. (More exact details of the electrocardiographic criteria derived by us can be seen in table 6, which will be discussed later.) The greater

7. (*a*) Herrick, J. B.: Thrombosis of the Coronary Arteries, J. A. M. A. **72:** 387 (Feb. 8) 1919. (*b*) Smith, F. M.: Electrocardiographic Changes Following Occlusion of the Left Coronary Artery, Arch. Int. Med. **32:**497 (Oct.) 1923. (*c*) Kahn, M. H.: The Electrocardiographic Signs of Coronary Thrombosis and Aneurysm of the Left Ventricle of the Heart, Boston M. & S. J. **187:**788, 1922. (*d*) Clarke, N. E., and Smith, F. J.: The Electrocardiogram in Coronary Thrombosis, J. Lab. & Clin. Med. **11:**1071, 1925. (*e*) Pardee, H. E. B.: Heart Disease and Abnormal Electrocardiograms, with Special Reference to Coronary T-Wave, Am. J. M. Sc. **169:**270, 1925. (*f*) Barnes, A. R.: The Electrocardiographic Localization of Myocardial Infarcts, M. Clin. North America **14:**671, 1930; (*g*) Q and T Types of Electrocardiograms: Their Comparative and Complementary Value in Indicating Occurrence of Acute Myocardial Infarction, Am. Heart J. **9:**722, 1934. (*h*) Barnes, A. R., and Whitten, M. B.: Study of the R-T Interval in Myocardial Infarction, ibid. **5:**142, 1929. (*i*) Willius, F. A., and Barnes, A. R.: Myocardial Infarction: An Electrocardiographic Study, J. Lab. & Clin. Med. **10:**427, 1925. (*j*) Barnes, A. R.: Correlation of Initial Deflections of Ventricular Complex with Situation of Acute Myocardial Infarction, Am. Heart J. **9:**728, 1934. (*k*) Parkinson, John, and Bedford, D. E.: Successive Changes in the Electrocardiogram After Cardiac Infarction, Heart **14:**195, 1928. (*l*) Levine, Samuel A., and Brown, C. L.: Coronary Thrombosis: Its Various Clinical Features, Medicine **8:**245, 1929. (*m*) Stewart, H. J.: The Relation of Clinical, Including Electrocardiographic, Phenomena to Occlusion of the Coronary Arteries Based on the Observation of a Case, Am. Heart J. **4:**393, 1929. (*n*) Gilchrist, A. R., and Ritchie, W. T.: The Ventricular Complexes in Myocardial Infarction and Fibrosis, Quart. J. Med. **23:**273, 1930. (*o*) Nathanson, M. D.: Electrocardiogram in Coronary Disease, Am. Heart J. **5:**257, 1930. (*p*) Cooksey, W. D., and Freund, H. A.: Serial Electrocardiographic Studies in Coronary Thrombosis, ibid. **6:**608, 1931. (*q*) Fenichel, N., and Kugell, V.: The Large Q-Wave of the Electrocardiogram: A Correlation with Pathological Observations, ibid. **7:**235, 1932. (*r*) Winternitz, M.: The Initial Complex of the Electrocardiogram After Infarction of the Human Heart, ibid. **9:**616, 1934. (*s*) France, R.: The Large Q-Wave in Lead III of the Electrocardiogram, Am. J. M. Sc. **187:**16, 1934. (*t*) White, Paul D.: Electrocardiographic Evidence of Recent Coronary Thrombosis Superimposed on Bundle-Branch Block Resulting from Previous Coronary Disease, Am. Heart J. **10:**260, 1934. (*u*) Appelbaum, E., and Nicolson, G. H. B.: Occlusive Disease of the Coronary Arteries, ibid. **10:** 662, 1935. (*v*) Saphir, O.; Priest, W. S.; Hamburger, W. W., and Katz, L. N.: Coronary Arteriosclerosis, Coronary Thrombosis and the Resulting Myocardial Changes, ibid. **10:**567, 1935. (*w*) Jervell, Anton: Elektrokardiographische Befunde bei Herzinfarkt, Acta med. Scandinav., supp. 68, 1935, p. 1. Wilson and others.[1d] Hoffman and Delong.[1e] Wolferth, Wood and Bellet.[4b]

number of the 200 cases of our series were therefore fitted into one of these two groups according to the evidence afforded by the four lead electrocardiograms. A small number of cases were placed in a group designated as instances of combined anterior and posterior infarcts (one of the infarcts being recent). The basis for this third classification was either autopsy evidence of a combination of infarcts or, when autopsy was not performed, conclusive evidence in serial records of sudden coronary closure on two or more distinct occasions, with infarction in two regions.

(*c*) *Method of Analysis.*—The frequency of the various abnormalities in each of the four leads was determined for the foregoing groups. For purposes of comparison the cases were divided into three series: series A, consisting of the entire 200 consecutive cases; series B, consisting of the cases in which death was known to have occurred, and series C, consisting of the cases in which the diagnosis was verified at autopsy.

THE MANNER IN WHICH THE CHEST LEADS WERE TAKEN

There is still considerable confusion concerning the manner in which the chest lead should be taken, as regards (1) the size of the chest electrode, (2) the placement of the chest and distant electrodes, (3) the manner of connecting the electrodes to the galvanometer and (4) the manner of designating the lead.

Fortunately, many of these points have been clarified by experience. Thus it is almost universally agreed that the right arm terminal should be connected to the chest electrode and the left leg terminal to the distant electrode, a method which we have used consistently and which we urge as a universal practice. There is no logical reason for making the reverse connection, recently urged, since the connections are purely a matter of convention.

Although Wolferth and Wood [1a] originally placed the distant electrode on the posterior part of the chest, they found that the variations in the contour of the chest lead are but little affected by a change in position of the distant electrode, so long as this is not brought too close to the heart. This is confirmed by our own experience and that of others. The electrode nearest the heart dominates the curve. For convenience we have used the left leg electrode as the distant electrode in our work. We see no theoretical advantage and some practical disadvantages in the use of the special distant electrode suggested by Wilson and his colleagues.[8]

The location of the chest electrode is of considerable importance. A small shift in its position will alter the record considerably. Hence,

8. Wilson, F. N.; Johnston, F. D., and Hill, I. G. W.: The Interpretation of the Galvanometric Curves Obtained When One Electrode Is Distant from the Heart and the Other Near or in Contact with the Ventricular Surface: I. Observations on the Cold Blooded Heart, Am. Heart J. **10**:163, 1934; II. Observations on the Mammalian Heart, ibid. **10**:176, 1934.

a fixed position with respect to some bony structure seems desirable to insure consistency when successive records are taken. We have not found it satisfactory to place the chest electrode over the apex of the heart, as is done in some clinics. The apex is not a fixed point in relation to the chest or to the parts of the heart. It may alter its location considerably from time to time even in the same patient, and it cannot always be accurately determined. The variability in these factors makes

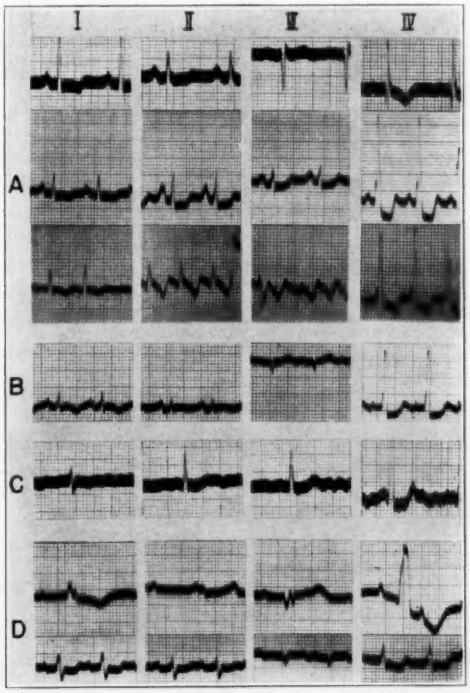

Fig. 2.—Electrocardiograms of 4 patients (cases A to D) with proved infarction of the anterior wall due to slowly occluding or narrowing sclerotic plaques in the left anterior descending coronary artery associated with sclerotic changes in the right coronary artery. The necropsy reports are summarized in table 3.

Case A	Case B	Case C	Case D
Curve taken before attack 10/25/35	Attack..... 4/25/33	Attack..... 11/ 1/34	Attack..... 8/27/32
Attack..... 12/15/35	Curve taken. 5/31/33	Curve taken. 12/21/34	Curves taken 9/ 1/32
Curves taken 12/18/35	Death..... 6/ 2/33	Death..... 1/16/35	9/12/32
12/26/35			Death..... 9/16/32
Death..... 12/31/35			

this type of chest lead occasionally confusing. After considerable experimentation we have found that for the vast majority of patients the most favorable application of the chest electrode is just to the left

of the sternal margin in the fourth intercostal space. This single chest contact is in our experience by far the most informative. Chest leads taken in this manner are fairly uniform for normal adults. In cases of coronary disease this chest lead is particularly useful, since it depicts the events in an area of the heart which is sometimes not recorded in the conventional three leads. This site on the chest is free from intervening lung and has three sides marked by bony structures. We have investigated various sites on the chest in many of our cases and have found that only occasionally in instances of posterior infarction will changes be detectable with the electrode in the left anterior axillary line and not demonstrable with the electrode in the left parasternal position.

Within reasonable limits the size of the chest electrode makes little difference. For technical simplicity we have used the same electrodes for the chest as those employed for the extremities (1½ by 2½ inches [3.8 by 6.4 cm.]).

A great deal of confusion at present exists because of differences in nomenclature. We believe it will simplify matters if the term lead IV is restricted to a lead connecting the chest with a distant electrode. This should be amplified by describing the location of the chest electrode. Thus, we describe our lead IV as follows: lead IV (fourth interspace, left parasternal line—left leg).

RESULTS

(*a*) *Incidence and Mortality.*—In our series there were over three times as many men as women (table 1). This greater frequency in men is in accord with the findings reported by others.[9] The mortality rate was about the same for each sex.

The average age at which the attacks occurred was 55 years for our entire series of patients and but little more for those that died (57 years). The scatter of the age incidence was wide (table 1), but the greater number of attacks occurred in the fifth decade. This is also in close agreement with the findings of others.[10] Death occurred more often in the sixth decade.

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9. (*a*) Levy, H., and Boas, E. P.: Coronary Artery Disease in Women, J. A. M. A. **107**:97 (July 11) 1936. (*b*) Conner, Lewis A., and Holt, E.: The Subsequent Course and Prognosis in Coronary Thrombosis, Am. Heart J. **5**:705, 1930. (*c*) Polanco, Mario: The Relation of Coronary Sclerosis to Symptoms and Its Distribution in Two Hundred and Forty-Two Fatal Cases, Am. J. M. Sc. **192**:840, 1936. (*d*) Levine and Brown.[71]

10. (*a*) Barnes, A. R., and Ball, R. G.: The Incidence and Situation of Myocardial Infarction in One Thousand Consecutive Postmortem Examinations, Am. J. M. Sc. **183**:215, 1932. (*b*) Mullins, W. L.: Age Incidence and Mortality in Coronary Occlusion, Pennsylvania M. J. **39**:322, 1936. (*c*) Levine and Brown.[71] Appelbaum and Nicolson.[7u] Conner and Holt.[9b] Polanco.[9c]

The data pertaining to mortality have been assembled in table 2. It is significant that the known mortality is highest in cases of combined anterior and posterior infarctions, since it has already been established that death is more frequent after a second or third closure.[11] The mortality is higher during the first few weeks after the attack than later. Delayed death was frequently associated with another attack.

(*b*) *Detailed Report of the Cases in Which Recent Infarction Was Shown at Autopsy.*—There have been so few reports of cases of recent infarction in which the diagnosis was verified at autopsy and in which

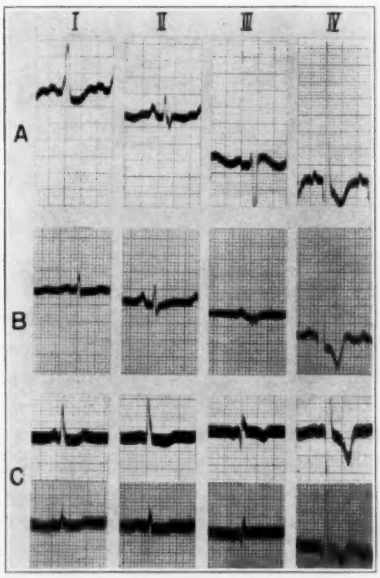

Fig. 3.—Electrocardiograms of 3 patients (cases A to C) with proved infarction of the anterior wall due to slowly occluding or narrowing sclerotic plaques in the left anterior descending coronary artery associated with sclerotic changes in the right coronary artery. The necropsy reports are summarized in table 3.

Case A		Case B		Case C	
Attack.....	12/30/34	Attack.....	2/24/36	Curve taken before attack.	5/ 7/36
Curve taken.	1/ 3/35	Curve taken.	2/25/36	Attack.....	5/29/36
Death.....	1/22/35	Death.....	3/ 8/36	Curve taken.....	5/31/36
				Death.....	5/31/36

four lead electrocardiograms were made that the details of these 25 cases are placed on record. The necropsy data, based on the report of

11. (*a*) Master, A. M.; Jaffe, H. L., and Dack, S.: Multiple Attacks of Coronary Artery Thrombosis, Am. Heart J. **12**:244 (Aug.) 1936. (*b*) Wilson and others.[1d] Goldbloom.[1g]

Dr. O. Saphir, of the department of pathology, were analyzed and are shown in table 3, and the electrocardiographic records are shown in figures 1 to 7. These 25 cases include 15 cases of recent anterior infarction (figs. 1 to 3), 4 cases of recent posterior infarction (fig. 4) and 6 cases of combined anterior and posterior infarctions, one of the infarcts being recent (figs. 5 to 7).

(*c*) *Frequency of Types.*—As table 4 shows, recent anterior infarction occurred more often than either of the other two types, both in the entire series of 200 cases and in the 25 cases in which autopsy was performed. The greater incidence of the anterior type is in accord with that shown in other reports.[12] This study shows further that infarcts are more correctly localized when all four leads are analyzed than when the analysis is confined to conventional leads, since the incidence of anterior and of posterior infarct based on four lead electrocardiograms correponds much more closely with postmortem reports than the incidence based on three lead electrocardiograms. The smaller number of recent posterior infarcts in the series of cases in which autopsy was performed as compared with the greater number of this type in the entire series is in accord with the prevailing opinion that for posterior infarcts the mortality rate is lower than for anterior infarcts.

The combined infarction was the least common variety, but in the series of cases in which autopsy was performed it was six times more frequent than in the entire series (table 4). In part this difference in frequency is an indication that the lesions giving rise to two infarcts are more apt to be fatal than those causing single infarcts. This is in accord with past experience.[13] In part the difference may be due to the occasional difficulty of establishing a correct diagnosis from the electrocardiograms. We classified cases in which autopsy was not performed as belonging in this group only when serial curves demonstrated both occlusions (fig. 11 *A* and *B*). Since in the cases of combined infarcts demonstrated at autopsy the most recent infarct dominated the final electrocardiographic curve (figs. 5 and 6 *B*), it is probable that in a number of cases in which autopsy was not done and in which there was more than one infarct either the condition was classed as a single anterior or posterior infarct or the case was rejected from the series because the diagnosis was not established. This is a possible source of error in the interpretation of single electrocardiograms.

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12. (*a*) Sprague, Howard B., and Orgain, Edward S.: Electrocardiographic Study of Cases of Coronary Occlusion Proved at Autopsy at the Massachusetts General Hospital (1914-1934), New England J. Med. **212**:903, 1935. (*b*) Levine and Brown.[7l] Appelbaum and Nicolson.[7u] Barnes and Ball.[10a] Mullins.[10b]

13. Conner and Holt.[9b] Master, Jaffee and Dack.[11a] Sprague and Orgain.[12a]

(*d*) *The Relative Value of the Different Leads in the Diagnosis of Recent Infarction.*—In 64 per cent of the entire series of 200 cases the electrocardiograms showed characteristic changes in all four leads, in 32.5 per cent there were one or more leads in which the changes were not typical, and in 3.5 per cent there was a single record which though abnormal was not characteristic, the diagnosis being based on the change

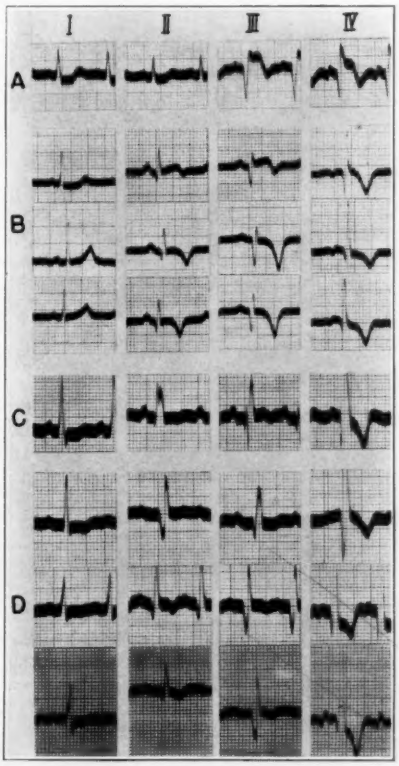

Fig. 4.—Electrocardiograms of 3 patients (cases A to C) with infarction of the posterior wall due to a thrombus in the circumflex branch of the right coronary artery. Also electrocardiograms of a patient (case D) with proved infarction of the posterior wall with septal extension due to sclerotic involvement of both coronary arteries. The necropsy reports are summarized in table 3.

Case A		Case B		Case C		Case D	
Attack.....	5/ 4/36	Attack.....	7/12/32	Attack.....	4/ 3/35	Curve taken before attack	2/ 1/35
Curve taken.	5/ 6/36	Curves taken	8/ 3/32	Curve taken.	4/ 9/35	Attack.....	11/17/35
Death.....	5/ 8/36		8/29/32	Death.....	7/13/35	Curves taken	11/22/35
			9/24/33				11/25/35
		2d attack....	9/24/33			Death.....	11/27/35
		Death.....	10/ 1/33				

observed in the serial curves. In 16 per cent of the cases in which autopsy was performed the electrocardiogram was not characteristic (in all these cases only one record was made [figs. 1 to 7, inclusive]). This indicates that we probably failed to recognize instances of recent infarction when only one record was taken.[14]

In 26 per cent of the 200 cases the conventional leads were not characteristic in single or in serial curves, the diagnosis being based primarily on the changes in lead IV. In only 6.5 per cent were the conventional leads characteristic and lead IV without characteristic changes. The fact that more than a fourth of all the cases might have been overlooked (even in a study of serial curves) if the diagnosis had depended only on the standard three leads shows the value of lead IV and points to the need of taking this lead in all cases of suspected recent infarction. This is particularly true of cases of anterior infarctions, lead IV having established the diagnosis in 30.3 per cent of these instances in our series. Furthermore, lead IV was often of great value in confirming the diagnosis in instances of combined anterior and posterior infarctions. However, lead IV did not establish the diagnosis in 2.5 per cent of the cases of anterior infarction and in 12.3 per cent of the cases of posterior infarction. In cases of posterior infarction lead III was frequently the lead which determined the diagnosis early.

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14. On the other hand, we noted 1 case in which autopsy failed to show infarction and in which infarction was indicated clinically and electrocardiographically two years before death (fig. 10 *C*). This patient at autopsy showed only narrowing of both coronary arteries, but no occlusion or myocardial infarction could be seen. Whether we were dealing with disseminated small infarcts (Büchner, F.; Weber, A., and Haager, B.: Koronarinfarkt und Koronarinsuffizienz, Leipzig, Georg Thieme, 1935. Büchner, F., and von Lucadou, W.: Electrocardiographische Veränderungen und disseminierte Nekrosen des Herzmuskels bei experimentellen Coronarinsuffizienz, Beitr. z. path. Anat. u. z. allg. Path. **93**:168, 1934) is problematic. Small multiple infarcts do occur (viz., cases illustrated in figure 8 *A* and *B*). When they heal, the scars which form, it seems to us, would be difficult to distinguish post mortem from fibrosis which gradually develops without infarction, yet the electrocardiogram would show the localized ischemia (Feil, H. S.; Katz, L. N.; Moore, R. A., and Scott, R. W.: The Electrocardiographic Changes in Myocardial Ischemia, Am. Heart J. **6**:522, 1931. Katz, L. N., and Wallace, A. W.: The Role of Cardiac Ischemia in Producing R-T Deviations in the Electrocardiogram, Am. J. M. Sc. **181**:836, 1931. Kountz, W. B., and Hammonda, M.: The Effect of Asphyxia and of Anoxemia on the Electrocardiogram, Am. Heart J. **8**:259, 1932. Rothschild, M. A., and Kissin, M.: Induced General Anoxemia Causing R-T Deviation in the Electrocardiogram, ibid. **8**:745, 1932) and would have a time course similar to that in cases of confluent infarction. We have noted another case in which there were suggestive changes but coronary involvement was not observed at autopsy. Here the changes seen in the electrocardiogram (fig. 8 *C*) were probably associated with the moribund condition of the patient at the time the records were taken.

Digitalis in large doses tends to modify the form of the electrocardiogram,[15] but in only 9 per cent of our series of 200 cases was digitalis given, usually in too small quantities to interfere with the electrocardiographic interpretation. In fact, it was found that in only 1 case had large quantities of digitalis been given with resulting confusion (fig. 1 *H*).

Intraventricular block was another disturbing element in the evaluation of the electrocardiographic changes,[16] as was also the effect of old, long-standing coronary insufficiency. In these instances serial curves are of great value. Pericardial involvement also may distort the elec-

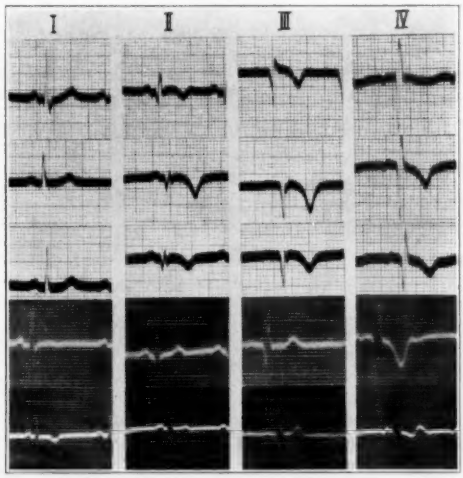

Fig. 5.—Electrocardiograms of a patient with proved old infarction of the posterior wall and recent infarction of the anterior wall. The necropsy reports are summarized in table 3.

First attack	7/20/32	Second attack	12/ 8/33
Curves taken	8/ 3/32	Curves taken	12/ 9/33
	8/27/32		12/20/33
	9/19/32	Death	12/23/33

15. DeGraff, A. C., and Wible, C. L.: Production by Digitalis of T-Wave Changes Similar to Those of Coronary Occlusion, Proc. Soc. Exper. Biol. & Med. **24**:1, 1926. Brams, W. A., and Gaberman, P.: The Effect of Digitalis on the T-Wave of the Electrocardiogram: An Experimental Study in Human Beings, Am. Heart J. **6**:804, 1931. Strauss, H., and Katz, L. N.: Effect of Digitalis on the Appearance of Lead IV, ibid. **10**:204, 1935.

16. Salcedo-Salgar, Jorge, and White, Paul D.: The Relationship of Heart-Block, Auriculoventricular and Intraventricular, to Clinical Manifestations of Coronary Disease, Angina Pectoris and Coronary Thrombosis, Am. Heart J. **10**:1067, 1935. Ball, David: The Occurrence of Heart-Block in Coronary Artery Thrombosis, ibid. **8**:327, 1932. White.[7t]

trocardiogram.[17] Pulmonary embolism also caused difficulties, and we have recently observed 2 cases in which the electrocardiographic distortion was due to nonpenetrating thoracic trauma. The problem of differentiating cardiac insufficiency on the basis of advanced coronary sclerosis from abrupt coronary closure was met with a number of times and was not always easy to solve. Again we have found, as we pointed out in a previous communication,[1h] that in a case of chronic coronary insufficiency a single record may show a picture (fig. 10 *A*) similar to that seen in cases of abrupt coronary closure; serial curves, however, will fail to show the regression indicative of healing seen after an infarct develops.

(*e*) *Abnormalities in Standard Three Leads in Cases of Recent Infarction.*—Our analysis of these changes are summarized in table 4 and are illustrated by serial curves in figures 12 *A*, 13, 14 and 17 and by the curves for the cases in which autopsy was performed (figs. 1 to 7). The following points merit emphasis:

1. Abnormalities of rhythm occurred occasionally, especially in cases of the anterior type of infarct (figs. 1 *H*; 2 *A*, curve 3, and 2 *C*).

2. Intraventricular block occurred especially in cases of combined infarcts (figs. 6 *A* and *B* and 7 *C*). It was observed also in 3 cases of anterior infarction in which autopsy was performed (figs. 1 *F* and *G* and 2 *D*). Thus while septal infarction occurred in 64 per cent of all cases in which autopsy was performed (table 3), electrocardiographic evidence of intraventricular block occurred in only 40 per cent of these same cases. However, septal infarcts do not always lead to intraventricular block, as shown by our group of cases in which autopsy was performed, especially those in which the condition involved only the apex or the lowest third of the septum. In the present series there was 1 case of intraventricular block without septal infarction (fig. 6 *B*), probably on the basis of old coronary sclerosis. Intraventricular block often masks the features of the electrocardiogram commonly seen with infarction (figs. 1 *F*, curve 2, and 2 *D*). Often, despite the block, changes occur which indicate an occlusion, especially when serial curves are obtained. At all events, a succession of changes or the presence of transitory block is to be viewed as suggestive.

17. Scott, R. W.; Feil, H. S., and Katz, L. N.: Electrocardiogram in Pericardial Effusion: I. Clinical, Am. Heart J. **5**:68, 1929. Katz, L. N.; Feil, H. S., and Scott, R. W.: Electrocardiogram in Pericardial Effusion: II. Experimental, ibid. **5**:78, 1929. Barnes, A. R.: Electrocardiographic Pattern Observed Following Coronary Occlusion Complicated by Pericarditis, ibid. **9**:734, 1934.

3. Low "voltage" in the conventional leads was a frequent finding, especially with recent anterior infarcts,[18] and was not usually associated with low voltage in lead IV (figs. 1 *A* to *D*, *G*, *H*; 2 *B* and *D*, and 3 *C*). At times this low voltage was transitory.

4. Slurring or notching of QRS occurred in almost all cases.

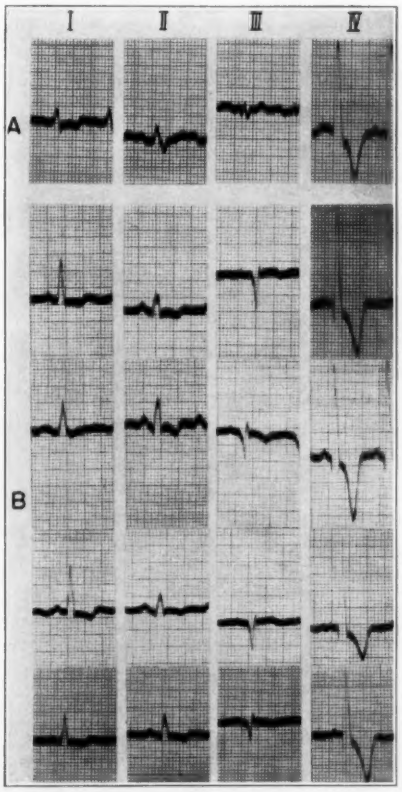

Fig. 6.—Electrocardiogram of a patient (case A) with proved old infarction of the anterior wall and recent infarction of the posterior wall and electrocardiograms of a patient (case B) with proved old infarction of the anterior wall and more recent infarction of the posterior wall (about two months old at the time of death). The necropsy reports are summarized in table 3.

Case A		Case B	
Attack	2/19/36	First attack	1/ 3/36
Curve taken	2/26/36	Curve taken	2/ 6/36
Death	2/26/36	Second attack	3/13/36
		Curves taken	3/14/36, 3/23/36, 4/15/36
		Death	4/27/36

18. Steuer, L. G.: The Electrocardiogram of Low Voltage: A Report of Fifty Autopsied Cases, Am. Heart J. **9**:405, 1934.

5. Left axis shift occurred with all types, but the marked deviation associated with preponderance of the left ventricle was more common with posterior infarction (table 4). On occasion this was transitory.[19]

6. Right axis shift was infrequent and in our series occurred only with anterior infarction. On occasion it was transitory.

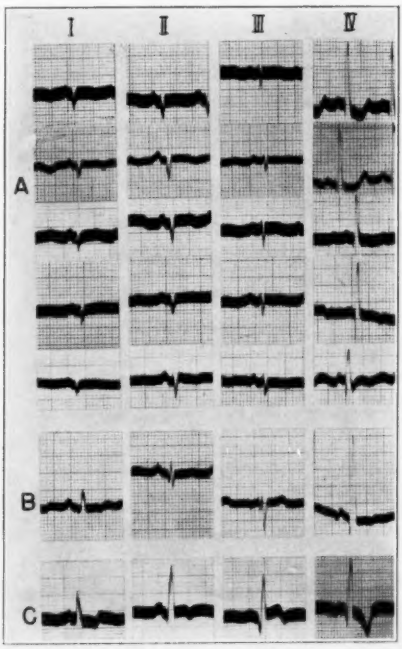

Fig. 7.—Electrocardiograms of 2 patients (cases A and B) with proved old infarction of the posterior wall, with more recent infarction of the anterior wall, the latter due in both cases to the occurrence of thrombi in the left anterior descending coronary artery a few months before death. The third electrocardiogram is that of a patient (case C) with proved old infarction of the anterior wall due to an occluding plaque in the left anterior descending coronary artery and an old and more recent infarction of the posterior wall due to old narrowing and a recent thrombus in the right coronary artery. In all 3 cases there were aneurysms in the infarcted areas. The necropsy reports are summarized in table 3.

Case A		Case B		Case C	
Attack.....	2/ 7/36	Attacks of pain for two years		Attacks of pain for several years	
Curves taken.	3/ 5/36	Last attack.....	10/19/32	Last attack.....	1/18/34
	3/11/36	Curve taken.....	10/25/32	Curve taken.....	1/19/34
	4/ 9/36	Death.....	10/31/32	Death.....	1/20/34
	4/27/36				
	5/ 5/36				
Death.....	5/ 8/36				

19. Bartels, E. C., and Smith, H. L.: Gross Cardiac Hypertrophy in Myocardial Infarction, Am. J. M. Sc. **184**:453, 1932.

7. Deviations in the ST segment were not always characteristic. With anterior infarction the classic change is said to be an elevated ST segment in lead I (fig. 15). In our series depression of the ST segment in lead I was more than twice as common as elevation of this segment with anterior infarction (series A, table 4). In 6 of the 8 cases in which autopsy was performed recent anterior infarctions due to thrombotic closure had an elevated ST_1 (fig. 1 *A* to *D, F* and *G*), while those due to closures resulting from sclerotic plaques did not show any elevation of ST. In fact, in 5 of 7 of the latter cases ST_1 was depressed (figs. 2 *A, B* and *D,* and 3 *A* and *B;* table 4, series C). In the entire series of cases of posterior infarction the classic picture of depression of ST_1 was common (table 4, series A) and occurred in every case in which autopsy was performed (fig. 4 *A* to *D*); an elevated ST_1 occurred

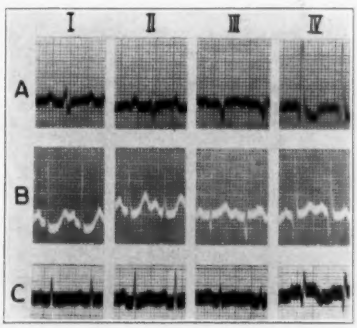

Fig. 8.—Electrocardiograms of 2 patients (cases A and B) with multiple small infarctions. Both coronary arteries had sclerotic plaques. Necropsy reports are summarized in table 3. In case C autopsy showed no infarction or coronary involvement even on microscopic examination, so the electrocardiographic changes may be explained as probably due to terminal ischemia of the myocardium of a dying patient.

Case A		Case B		Case C	
Repeated attacks of pain for fifteen months		Vague cardiac pain for several years		Prostatectomy.	11/28/33
Severe attack	12/31/35	Severe attack.	12/ 3/34	Curve taken	12/15/33
Curve taken	1/ 7/36	Curve taken	12/ 4/34	Death	12/18/33
Death (pulmonary embolism)	1/16/36	Death	12/13/34		

in only 5.5 per cent of the entire series of cases of posterior infarction. Of the 6 cases of combined infarcts in which autopsy was performed, the ST_1 segment was depressed in 4 (figs. 6 *A* and *B* and 7 *B* and *C*) and was unchanged in the other 2 (figs. 5 and 7 *A*). The changes in the ST segment in lead II were extremely variable. The classic picture of elevation of ST in lead III with posterior infarction was common in the entire series (table 4, series A) and occurred in all the cases of this type of infarction in which autopsy was performed (fig. 4 *A* to *D*). How-

ever, in 6.8 per cent of the cases of posterior infarction in the entire series the ST segment in lead III was depressed (table 4, series A). With the combined type there was elevation of ST_3 in 2 cases in which autopsy was performed (figs. 6 *B* and 7 *C*). These were cases in which a more recent posterior infarct was due to a thrombus in the right coronary artery. The classic picture of depression of the ST segment in lead III with anterior infarction occurred in only 26.9 per cent of the entire series, and in an almost equal number (25.2 per cent) the ST segment was elevated in this lead (table 4, series A). The series of cases in which autopsy was performed demonstrate that the elevation of ST_3

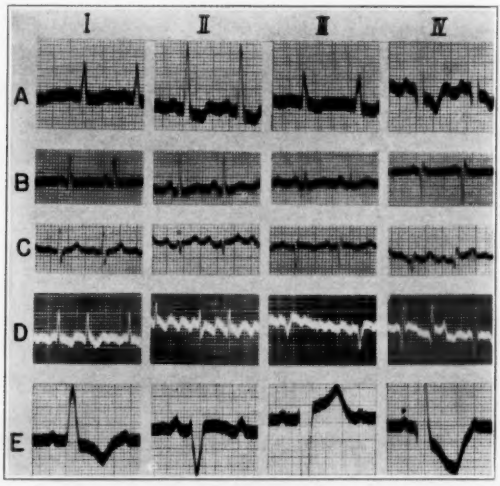

Fig. 9.—Electrocardiograms of 5 patients (cases A to E) with proved coronary sclerosis without infarction. The necropsy reports are summarized in table 3.

Case A		Case B		Case C	
Attack	11/ 5/35	Operation	9/ 7/35	Herniotomy	2/ 6/35
Curve taken	11/21/35	Curve taken	9/10/35	Curve taken	2/13/35
Death	11/24/35	Death	9/18/35	Death	2/22/35

Case D		Case E	
Cholecystectomy	7/ 9/35	Curve taken	2/24/34
Severe pain	8/23/35	Death (perforated duodenal ulcer)	4/ 9/36
Curve taken	9/10/35		
Death	9/16/35		

with anterior infarction was noted when closure was due to sclerotic plaques, with involvement of both the right and the left coronary artery (figs. 2 *D* and 3 *A*). In both cases there was intraventricular block.

It may therefore be concluded from the analysis of cases in which the diagnosis was verified at autopsy that (1) the changes observed

in the ST segment fit the classic picture closely in cases of recent anterior or posterior infarction due to thrombotic closure and that (*2*) the deviations observed in the ST segment are variable in cases in which autopsy shows recent anterior infarction due to closure caused by sclerotic plaques. Apparently the variability in the changes in the ST segment with recent anterior infarction due to closure caused by sclerotic plaques is to be attributed to an insufficient coronary blood

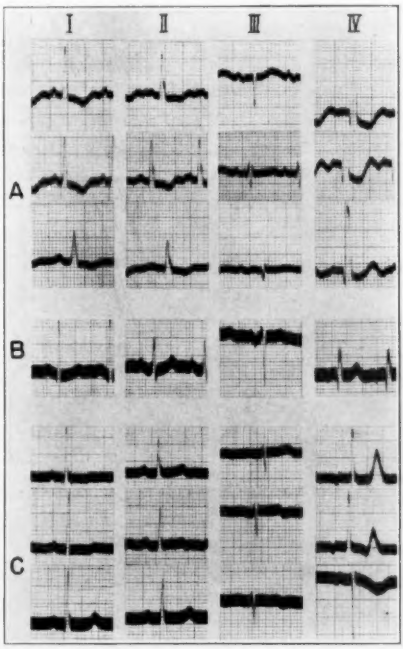

Fig. 10.—Electrocardiograms of 3 patients (cases A to C) with proved coronary sclerosis without infarction, resembling electrocardiograms of patients with infarction of the anterior wall. The necropsy reports are summarized in table 3. Case C is particularly interesting, since the clinical course in 1934 also indicated infarction.

Case A		Case B		Case C	
Curves taken.....	6/26/35	Prostatectomy.....	11/26/35	Curves taken....	2/ 3/34
	7/ 1/35	Pain in left side of chest.....	12/ 7/35		2/10/34
	7/29/35	Curve taken.....	12/27/35		2/23/34
Death (malignant nephrosclerosis)	8/ 2/35	Death (pulmonary embolism)	12/30/35	Cecostomy.....	3/ 1/36
				Death	3/ 3/36

supply to the posterior wall of the left side of the heart consequent on the diffuse coronary sclerosis in these cases. In the cases of closure due to sclerotic plaques the autopsy reports showed that the coronary

sclerosis was more extensive than in the cases of thrombotic closure and that the occluding plaques were often present in more than one artery (table 3).

The deviation of the ST segment in the classic picture [7k] is opposite in direction to that of the T wave. This deviation of the ST segment is often associated with bowing which points away from the peak of the T wave. According to the findings in cases in which autopsy was performed, this bowing appears in the earliest stages of the infarcts which are due to thrombosis but quickly disappears. With recent anterior infarction this bowing is up in lead I and down in lead III; with recent posterior infarction it is just the reverse (fig. 15). While the majority of the deviations in the ST segment tend to fit this picture, exceptions do occur, especially in cases of recent anterior infarct due to closure caused by sclerotic plaques. We have found further that, as has been shown in animal experiments,[20] the ST segment may be depressed in all three leads (fig. 2 *A*, curve 2) but is rarely elevated in all.

8. The coronary T wave, which may be positive or negative, as we have pointed out elsewhere,[21] is characterized by symmetrical limbs, rounded shoulders and a sharp peak,[7e] which may be associated with bowing and deviation of the ST segment in a direction opposite to that of the T wave.[7k] With recent anterior infarction the classic picture is a negative T wave in lead I and a positive T wave in lead III; with recent posterior infarction the direction of T in these leads is the reverse. The dominant T wave is found to occur during healing in the infarcted area.

A negative T_1 occurred in the majority of cases of recent anterior infarcts (table 4, series A); however, in approximately a fourth of these cases T_1 was upright.[22] A negative T_1 occurred only rarely with recent posterior infarction. A negative T_3 occurred in most instances of recent posterior infarction and was seen in every case in which the

20. Korey, H., and Katz, L. N.: The Electrocardiographic Changes Produced by Injuries of Various Parts of the Ventricles, Am. J. M. Sc. **188**:387, 1934. Smith, F. M.: The Ligation of Coronary Arteries with Electrocardiographic Study, Arch. Int. Med. **22**:8 (July) 1918. Crawford, J. H.; Roberts, G. H.; Abramson, D. I., and Cardwell, J. C.: Localization of Experimental Ventricular Myocardial Lesions by the Electrocardiogram, Am. Heart J. **7**:627, 1932. DeWaart, A.; Storm, C. J., and Koumans, A. K. J.: Ligation of the Coronary Arteries in Javanese Monkeys, ibid. **11**:676, 1936. Abramson, D. I.; Shookhoff, C., and Fenischel, N. M.: Study of Variations of RS-T Segment in Experimental Ventricular Trauma, ibid. **12**:174, 1936. Wood and Wolferth.[4e]

21. Bohning, A., and Katz, L. N.: Unusual Changes in the Electrocardiogram of Patients with Recent Coronary Occlusion, Am. J. M. Sc. **186**:39, 1933.

22. In these instances lead IV was the characteristic feature (figs. 12 *B* and 16 *A*).

lesion was present at autopsy (fig. 4). In approximately a sixth of the entire series of cases of recent posterior infarction, T_3 was upright. A negative T_3 occurred in 9.2 per cent of the cases of recent anterior infarction (table 4, series A). In the cases in which this lesion was present at autopsy, a negative T_3 occurred in only some of those in which the infarct was due to closure caused by sclerotic plaques (fig. 3 *A* to *C*), and it was not a typical coronary T wave. A negative T_2 was more often present with a negative T_3 than with a negative T_1.

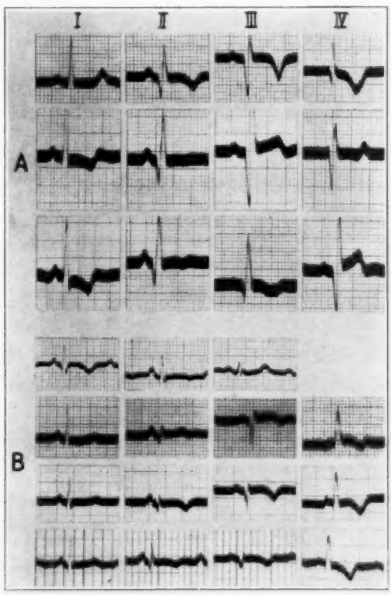

Fig. 11.—Electrocardiograms of a patient (case A) with case of combined infarction suggesting an old infarction of the posterior wall and more recent infarction of the anterior wall and electrocardiograms of a patient (case B) with combined infarction suggesting an old infarction of the anterior wall and a more recent infarction of the posterior wall.

Case A		Case B	
First attack	2/ 1/34	First attack	3/12/29
Curve taken	3/ 8/34	Curve taken	4/ 9/29
Second attack	5/ 1/35	Second attack	12/15/32
Curves taken	5/15/35	Curves taken	12/16/32
	1/ 2/36		12/29/32
Alive	6/ 1/36		1/26/33

Coronary T waves were more frequently seen when the waves were negative than when they were positive, but the reverse was true in several instances (figs. 4 *A* and *B*, 5 and 12 *B*). The changes in the T wave tended to conform with the classic picture, although exceptions

were not unusual, especially with anterior infarction due to closure caused by sclerotic plaques. A negative coronary T wave in all three leads did occur (fig. 14), but a positive coronary T wave in all three leads was rarely found.

9. The classic concept [3b] in regard to the Q wave (the term applied to the first negative phase of a diphasic QRS complex which is a fourth or more of the height of the major upright phase) and the S wave (a diphasic QRS complex with a negative second phase) was not confirmed in our series.

In our cases in which autopsy was performed the classic Q_1 occurred with recent anterior infarction due to thrombotic closure (fig. 1), but not in that due to closure with sclerotic plaques (figs. 2 and 3). A Q_1 did not occur in cases of recent posterior infarction (fig. 4).

In our cases in which autopsy was performed the classic Q_3 occurred in all instances of recent posterior infarction (fig. 4), but it occurred also in 3 instances of recent anterior infarction due to thrombotic closure (fig. 1 *C*, *D* and *H*). A Q_3 was also present in 3 cases of combined infarction shown at autopsy (figs. 5, 6 *B* and 7 *C*). A Q wave was found in all three leads on occasion (fig. 11 *B*).

The diagnostic value of Q_3 in the localization of infarcts is thus practically nil, and it is doubtful whether Q_1 is of greater value in this regard. Statistical studies have shown that Q_3 is found with a variety of types of chronic myocardial involvement other than infarction.[23] The weight of evidence seems to show that Q_3 indicates disease of the left ventricle, whether or not accompanied with recent (or old) infarction.[24] No significance could be attached to the occurrence of S_1 and S_3 in our series, except that S_3 never occurred in any cases in which recent

23. Bland, E. F., and White, P. D.: The Clinical Significance of Complete Inversion of Lead III in the Human Electrocardiogram, Am. Heart J. **6**:333, 1931. Kossman, C. E.; Shearer, M., and Texon, M.: Initial Ventricular Deflection in Electrocardiogram of Normal Subjects, ibid. **11**:346, 1936. Willius, F. A.: Occurrence and Significance of Electrocardiograms Displaying Large Q-Wave in Lead III, ibid. **6**:723, 1931. Edeiken, J., and Wolferth, C. C.: Significance of Deep Q in Lead III, ibid. **7**:695, 1932.

24. Pardee, H. E. B.: The Significance of an Electrocardiogram with a Large Q in Lead III, Arch. Int. Med. **46**:470 (Sept.) 1930. Goldbloom, A. A., and Kromer, M. L.: The Clinical Significance of the Deep Q-Wave in Lead III, M. Clin. North America **15**:1345, 1932. Wallace, A. W.: The Q-Wave in the Electrocardiogram, Am. J. M. Sc. **187**:498, 1934. Feldman, L.: The Initial Ventricular Complex of the Electrocardiogram in Coronary Thrombosis, Ann. Int. Med. **9**:1714, 1936. Strauss, Sidney and Feldman, L.: The Significance of Deep Q and Lead III, Am. J. M. Sc. **185**:87, 1933. Durant, T. M.: The Initial Deflections of the Electrocardiogram in Coronary Disease, ibid. **188**:225, 1934. Ziskin, T.: Clinical Significance of the Electrocardiogram with Large Q in Lead III, Arch. Int. Med. **50**:435 (Sept.) 1932. Barnes.[7g]

posterior infarction was noted at autopsy. No particular significance could be attached to the occurrence of the combination of Q_1 and S_3 or of Q_3 and S_1 in our series. The analysis of cases of proved recent infarction in our series and in the series of cases for which autopsy reports have been published does not support the concept that the Q and S waves are of much value in the diagnosis of recent infarction.

10. Further evidence of the reliability of the foregoing findings was afforded by a review of all the previously published electrocardiograms

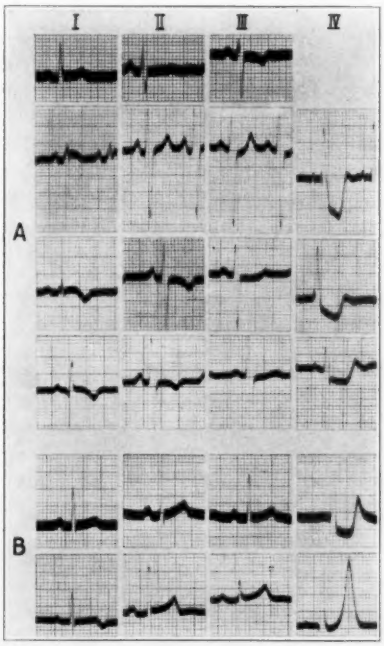

Fig. 12.—Electrocardiograms of 2 patients with recent anterior infarction. The serial curves in case A illustrate the classic type of change, especially early changes. Those in case B show marked changes in the T wave in lead IV.

Case A		Case B	
Curve taken before attack...	8/ 9/32	Attack.....	9/ 1/36
Attack.....	2/16/34	Curves taken.....	9/14/36
Curves taken.....	2/17/34		10/ 5/36
	3/ 2/34		
	11/13/34		
Death (no autopsy).....	10/13/34		

made in cases in which adequate autopsy reports of myocardial infarction were given. In some reports the manner of closure of the coronary artery, whether due to a fresh thrombus or to a sclerotic plaque, is not

designated, nor is the condition of the coronary arteries and myocardium adequately described. It is in such reports that statements are most often made that the changes in three lead electrocardiograms do not fit into the classically described criteria for anterior and posterior infarcts. On the other hand, there is an increasingly large literature with complete and carefully recorded clinical and necropsy data, which is of great value for correlations such as we have attempted. In checking over these published reports we have noted that the three lead electrocardiograms which fit the classically described types for recent anterior and recent posterior infarction most closely are almost invariably found in instances of a suddenly occluding coronary thrombus uncomplicated by old chronic lesions of the myocardium. The less typical three lead electrocardiograms occur in the group of reported cases in which the data show definite evidence of occluding sclerotic plaques or advanced sclerosis of both coronary arteries, with long-standing myocardial involvement. This confirms our own observations and emphasizes the importance of complete and accurate autopsy data in such cases.

(*f*) *Abnormalities in Lead IV with Recent Infarction.*—Our analysis of these changes is summarized in table 5. The following are the more significant findings:

1. A positive P wave was found more often in this series of cases than the normal negative or diphasic P_4; at times this positive P wave was transitory. However, the positive P wave was found associated with lesions other than coronary occlusion.

2. The presence or absence of the Q wave, the first negative phase of the QRS complex, has had considerable significance attached to it.[25] The absence of Q_4 has been stated to be characteristic in cases of recent anterior infarction. This is fairly well borne out in our cases in which autopsy was performed; in all cases of recent anterior infarction due to thrombotic closure this wave was absent (fig. 1), and in only 4 of the cases due to closure caused by sclerotic plaques was a small Q_4 wave seen (figs. 2 *C* and 3 *A* to *C*).

In the 4 cases of recent posterior infarction, on the other hand, the Q_4 wave was present (fig. 4 *A* to *C*), although it was small in the case associated with closure due to sclerotic plaques (fig. 4 *D*). It is noteworthy that Q_4 was present in all 6 cases of combined anterior and

25. Levine, Harold D., and Levine, Samuel A.: An Electrocardiographic Study of Lead IV, with Special Reference to the Findings in Angina Pectoris, Am. J. M. Sc. **191**:98, 1936. Faulkner, J. M.: The Electrocardiographic Diagnosis of Acute Cardiac Infarction, with Special Reference to the Value of Precordial Leads, New England J. Med. **213**:1215, 1936. Wilson and others.[1d] Johnston, Hill and Wilson.[3a] Wilson, Hill and Johnston.[3b]

posterior infarcts (figs. 5, 6 *A* and *B* and 7 *A* to *C*), even when the anterior infarct was the more recent (fig. 5). In the entire series, Q_4 failed to occur in a little more than half the 119 cases of recent anterior infarction; it was present in all 8 cases of combined infarction and was absent in only 6.8 per cent of the 73 cases of recent posterior infarction.

While the absence of Q_4 seems significant in cases of recent anterior infarction due to thrombotic closure, its presence does not rule out a recent anterior infarct. Furthermore, it must be borne in mind, as we

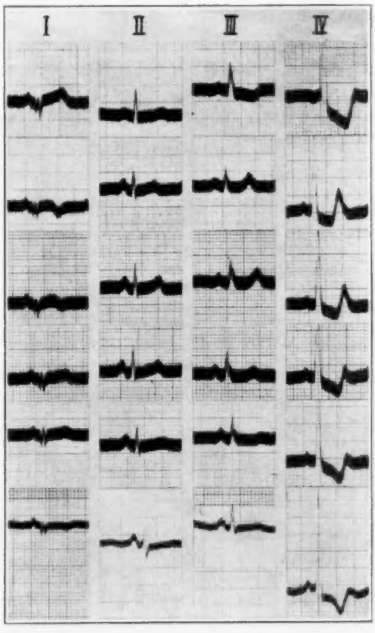

Fig. 13.—Electrocardiogram of a patient with anterior infarction. The serial curves illustrate the classic type of change and the late stages of recovery.

Attack	5/ 8/35	Curves taken	10/23/35
Curves taken	5/15/35		11/26/35
	6/12/35		2/21/36
	7/11/35	Alive	6/ 1/36

have reported before,[1h] that Q_4 may be absent when there is no infarction and even when there is no coronary disease.

3. The QRS complex, aside from a few instances of W-shaped or M-shaped complexes (usually associated with intraventricular block [26]),

26. Edeiken, J., and Wolferth, C. C.: Clinical Significance of M and W Shaped QRS Complex in Lead II of the Electrocardiogram, Am. J. M. Sc. **188**: 842, 1934.

was either monophasic and positive or diphasic. The diphasic QRS_4 had a negative first phase in most instances, but in a few the positive phase was first. Some of the diphasic QRS_4 complexes were mainly up, and a few were mainly down. As might have been anticipated from our discussion of the Q_4 wave, in all cases of proved recent anterior infarction due to thrombotic closure there was a monophasic upright QRS_4 (fig. 1), whereas in cases of recent anterior infarction proved to be due to closure caused by sclerotic plaques QRS_4 was not always monophasic (however, when not monophasic it was mainly up; figs. 2 and 3). In only 1 case of recent posterior infarction due to closure caused by sclerotic plaques was there a mainly upright QRS_4 (fig. 4 *D*). In the entire series QRS_4 was mainly or entirely up in about 75.7 per cent of the cases of recent anterior infarction and in only 12.3 per cent of the cases of recent posterior infarction (table 5). A mainly upright QRS_4 was also common with combined infarction. A mainly negative QRS_4 was found occasionally in cases of recent posterior infarction and was often transitory. The few instances in which there was a diphasic QRS_4 with a positive first phase occurred only in cases of recent anterior infarction and then this complex was sometimes associated with intraventricular block (fig. 1 *F*, curve 2, and *G*, curve 2).

In brief, this study indicates that a monophasic upright QRS_4 is characteristic of recent anterior infarction due to thrombotic closure but may occur in cases of infarction due to closure caused by sclerotic plaques. Furthermore, it must be borne in mind that an entirely or mainly positive QRS_4 occurs in cases of extensive coronary sclerosis without infarction (figs. 9 *A* and 10 *A* and *C*), as we have shown previously.[1h] It may therefore be a sign of extensive myocardial change and not necessarily of recent (or old) infarction.

4. Deviations in the ST segment were much more characteristic than the changes in the QRS complex. Elevation of ST_4 was seen in only 2 cases in which autopsy was performed and both were cases of recent posterior infarctions (fig. 4 *A* and *B*). Elevation of ST_4 occurred in 58.9 per cent of the entire series of cases of recent posterior infarction, in 3 of the 8 cases of combined infarction and in only 5.1 per cent of the entire series of cases of recent anterior infarction (table 5). Our study showed further that when ST_4 was elevated it tended to become horizontal, and its termination was more clearly to be differentiated than in the normal downward sloping ST_4 (fig. 4 *A*). This horizontal ST_4 often occurred without elevation, and we consider this a characteristic finding with recent posterior infarction (fig. 4 *B*).

A deeply negative ST_4 (more than 2 mm.) occurred in all but 1 of the cases of proved recent anterior infarction due to thrombotic closure (fig. 1), in 1 of the 6 cases of proved combined anterior and

posterior infarctions (fig. 6 *A* and *B*) and in 1 of the 4 cases of proved recent posterior infarction (fig. 4 *D*); in the last-mentioned case the infarct was due to closure caused by sclerotic plaques, and both coronary arteries showed advanced changes. In the entire series, a negative ST_4 of more than 2 mm. occurred in about 39.5 per cent of the cases of recent anterior infarction and in only about 6.8 per cent of the cases of recent posterior infarction (table 5).

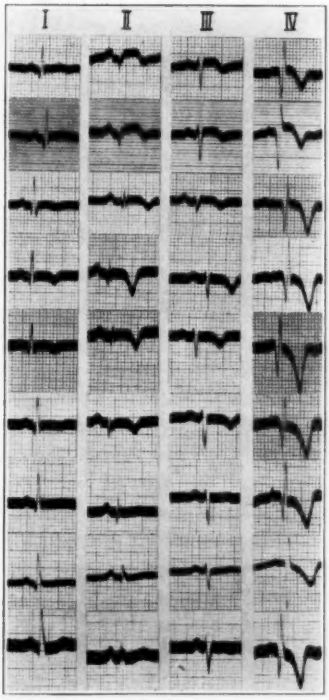

Fig. 14.—Electrocardiograms of a patient with recent posterior infarction. The serial curves illustrate the classical type of change.

Attack	8/12/32	Curves taken	10/22/32
Curves taken	8/17/32		2/28/34
	8/19/32		10/10/34
	8/26/32		3/26/36
	9/ 8/32	Alive	8/ 1/36
	9/15/32		

5. The T wave was characteristic in the majority of cases. A positive or diphasic T_4 was found in 40 per cent of the cases of proved recent anterior infarction (figs. 1 *C*, *D*, *F* and *G*, and 2 *A* to *D*) and not once in cases of proved recent posterior infarction. In the entire

series of 200 cases, positive and diphasic T waves were found in 77.3 per cent of the cases of recent anterior infarction and in only 9.6 per cent of the cases of recent posterior infarction. A T_4 within normal limits was found most often in cases of recent posterior infarction and of combined infarctions, and a deeply negative T_4 was found particularly in cases of recent posterior infarctions.

6. Thus, as in the case of the standard three leads, so in lead IV, in the cases in which autopsy was performed the recent infarctions due to thrombotic closure give more characteristic changes than those due to closure caused by sclerotic plaques. In all instances of recent infarction the changes in the ST segment and the T wave of lead IV are more informative than the changes in the QRS complex. Inspection of lead IV in other series of cases in which autopsy was performed shows that the facts here presented can be demonstrated also in these series. No one feature of lead IV can be considered an infallible sign of the type of infarction, although certain deviations of ST_4 and T_4 are fairly characteristic. Lead IV should be viewed in toto and should always be correlated with the standard three leads when a particular interpretation is being made, and the interpretation should be checked with serial curves.

(*g*) *The Value of Serial Four Lead Electrocardiograms in Cases of Recent Infarction.*—Our experience has shown that serial curves are often necessary before a final diagnosis can be made, and they are always helpful in estimation of the natural process and rate of progress of healing in the infarcted area and, perhaps as important as this, in determination of the amount of chronic coronary insufficiency remaining after the healing process has stopped. For these reasons we have paid particular attention to serial curves and have attempted a systematic electrocardiographic follow-up. This was not possible in every case. We were not able to follow through completely enough to obtain the entire series of electrocardiographic changes in all instances. Often it was difficult to obtain a curve immediately after the attack, because the patient was not hospitalized for several hours or days, but we have obtained a number of early curves. Again, it was not always possible to obtain records in the late stage of recovery, which sometimes extends over many months. However, we obtained a sufficient number of curves to be able to depict the usual course of these changes. On the basis of all these records, we have been able to reconstruct an idealized pattern of the succession of changes occurring with recent anterior infarction and those occurring with recent posterior infarction (fig. 15). No one series actually shows all these changes. Differences obviously exist from case to case (compare figs. 12 to 17). One should study the actual records

individually to see how the deviations in the electrocardiograms of different patients vary from the classic picture shown diagrammatically in figure 15. We have data for many other cases in which serial curves illustrate in one record or another all these changes, but space permits presentation of only a few. Figure 15 depicts merely the generalized pattern which is most common. On the evidence obtained from our own cases and from previously published reports of cases in which autopsy was performed, we have concluded that the characteristic picture shown in figure 15 occurs with recent infarction due to a sudden or thrombotic closure and that deviations from this picture are more likely to occur with infarction due to slowly occurring closure or closure caused by sclerotic plaques. No attempt has been made in the graph (fig. 15) to give the time values between stages, as the time span is an individual affair and varies widely. This is not surprising in view of the wide differences in the degrees of change within the myocardium and the variations in the recuperative efficiency of the coronary circulation of different hearts. The striking changes in the ST segment usually disappear rapidly, often in from a few hours to a few days. Obviously in not all cases is the record normal at first, as in figure 15, and in not all cases does it return to the preexisting level. Often, indeed, the record stops short of complete recovery and persists for a long period at one of the later stages.

The changes in figure 15 are for leads I, III and IV; lead II is omitted for clarity and because it is more variable in its appearance than the other leads. The changes in one lead do not always follow the same tempo as the changes in other leads. In some cases of recent posterior infarction the standard limb leads show the first characteristic change, but on the whole infarction is more easily diagnosed early from lead IV. We have also ignored the frequent transitory ebb and flow of fluctuations in electrocardiographic contour seen during the early stages. When several infarcts are present in different localities, naturally the development is not so typical. The presence of intraventricular block also confuses the picture, as does to a lesser extent the presence of other preexisting abnormalities that affect the electrocardiogram.

In the early stages of recent coronary occlusion the changes in the ST segment predominate. These have been described before, but we have attempted to correlate them and to depict them graphically. It will be seen that in cases of typical anterior infarction ST_1 becomes elevated, with an upward bowing and a rounded shoulder at the beginning of the T wave, and ST_3 is the inverted image of this. ST_4 at this time becomes deeply depressed and often horizontal, so that T_4 cannot be made out (fig. 15, stage 2). At the same time, Q_4 disappears (Q_1 and S_3 may or may not appear; figs. 12*A* and 13). In cases of poste-

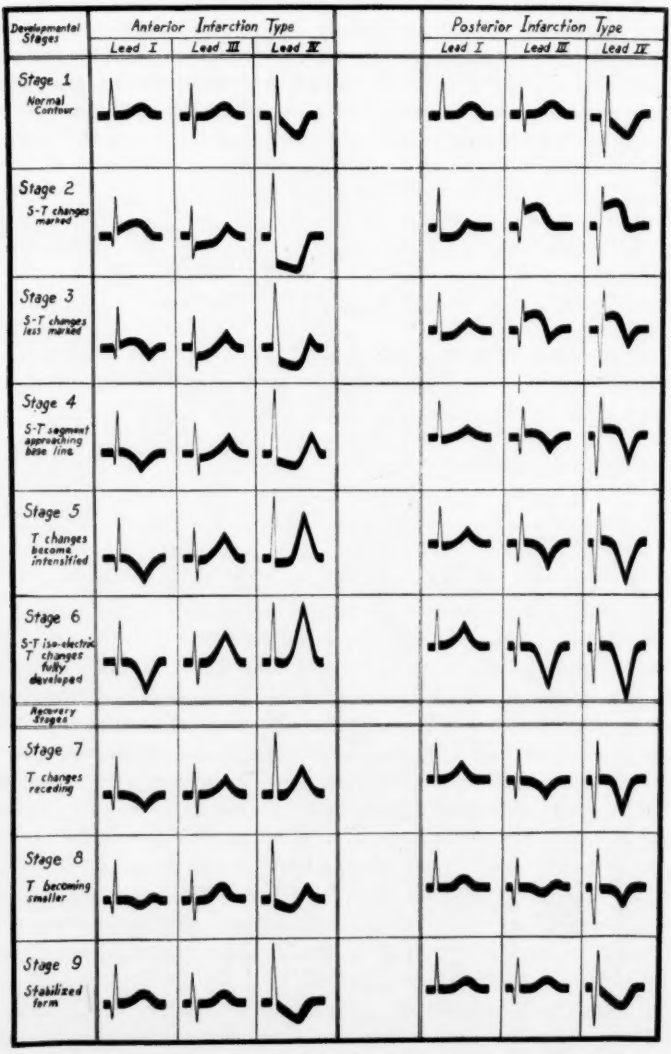

Fig. 15.—Diagrammatic illustration of classic type of changes usually found in leads I, III and IV in the stages of development of and recovery from uncomplicated infarctions of the anterior and of the posterior wall due to sudden thrombotic closures.

rior infarction the pictures in leads I and III are the reverse of those in cases of anterior infarction, except that Q_3 is more likely to appear. ST_4 becomes elevated (but not to the degree to which it sinks in cases of anterior infarction) and is horizontal or even bowed upward. As time goes on the ST segment with both types tends to return to the level of the iso-electric line; later the ST segment loses its bowing in the conven-

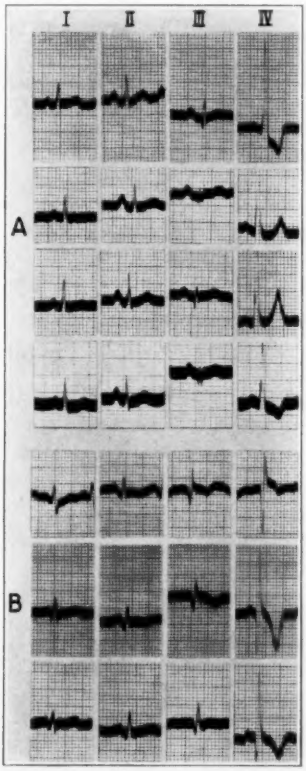

Fig. 16.—Serial electrocardiogram of a patient (case A) with anterior infarction in which typical changes occur in lead IV and nondiagnostic changes occur in the conventional leads. Serial electrocardiogram of a patient with posterior infarction in which the changes in lead IV (in ST and T) are typical, whereas the conventional three leads did not definitely establish the diagnosis.

Case A		Case B	
Attack	5/11/34	Attack	8/ 4/32
Curves taken	5/11/34	Curves taken	8/11/32
	5/22/34		8/15/32
	6/20/34		9/27/32
	9/23/36	Dropped dead several months later (no autopsy)	
Alive	10/—/36		

tional three leads, and a coronary T wave appears in these leads in a direction opposite to that of the original deviation of the ST segment (fig. 15, stages 3 to 5, and figs. 14 and 17). As we have previously emphasized, whether positive or negative, the coronary T wave is peaked and has symmetrical limbs and rounded shoulders. This coronary T wave waxes and becomes the dominant part of the record (fig. 15, stage

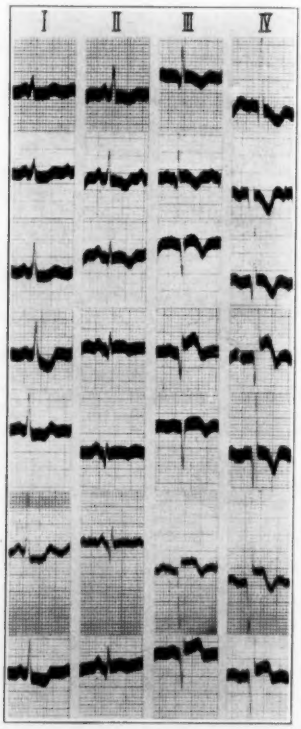

Fig. 17.—Serial electrocardiograms of a patient with posterior infarction, showing that the frequently recurring attacks of pain were accompanied with definite electrocardiographic changes.

Curve taken before attack...	10/ 9/35	Curves taken.....	11/12/35
Attack.....	10/15/35		12/12/35
Curve taken.....	10/16/35	Attack.....	12/27/35
Attack.....	10/26/35	Curves taken.....	12/30/35
Curve taken.....	10/28/35		2/ 4/36
Attack.....	11/12/35	Alive.....	6/ 1/36

6) before it wanes again and disappears. In cases of anterior infarction, as ST_4 returns toward the iso-electric or normally negative level and regains its downward declivity, a diphasic and then a positive T wave

appears, which waxes sometimes to great heights and then wanes and disappears (figs. 12 *B* and 16 *A*). In cases of posterior infarction the ST_4 segment returns to the iso-electric or normally negative level (less than 2 mm.) and regains its normal downward declivity; usually no clear evidence of infarction remains in this lead unless the T wave is deeply negative (figs. 14 and 16 *B*). Nevertheless, serial curves will reveal the progressive waxing and waning of T_4. The later changes (fig. 15, stages 7 to 9) are seen in only a limited number of cases. In some cases death occurs before these changes are fully developed, in others the electrocardiogram reaches a stationary form and in still others changes occur which may be interpreted (as we have previously shown [1h]) as indicating a progressive increase in the myocardial involvement due to coexisting progressing coronary disease.

Once the deviation in the ST segment disappears and only the deviations in the T wave remain, it becomes difficult to determine from a single record whether the electrocardiogram gives evidence of (*a*) an early stage of recovery after infarction in which T is waxing, (*b*) a late stage of recovery in which T is waning, (*c*) an old infarction or (*d*) chronic coronary insufficiency without infarction. Only the past clinical history can distinguish between *c* and *d*, and serial curves are required in order to distinguish *c* and *d* from *a* and *b*, and between *a* and *b*.

(*h*) *Speculations Concerning the Value of the Four Lead Electrocardiograms with Various Types of Coronary Insufficiency.*—The evidence presented in this report when correlated with that given in our earlier report on coronary sclerosis [1h] shows that the classification of coronary insufficiency given previously by us [1h] still holds and can be further amplified. Our experience shows that within certain limits serial four lead electrocardiograms can aid in the evaluation of the state and progress of the adequacy of the coronary circulation. They can serve to differentiate the transitory acute coronary insufficiency which leads to temporary electrocardiographic deformity without causing permanent injury to the myocardium (figs. 8 *C* and 10 *C*) from the more protracted coronary insufficiency which leads to infarction (figs. 2 and 3) and the less severe and more chronic forms which cause no infarction (fig. 9).

The time course of the different varieties of these forms of coronary insufficiency are depicted diagrammatically, with time as the abscissa and the degree of electrocardiographic deviation as the ordinate in figures 19 and 20. The characteristics of the various subgroups are summarized briefly in table 6.

In view of the findings in our own studies of cases and the autopsy evidence afforded by these and other cases, we now believe that coronary insufficiency may be subdivided as follows:

I. Subacute coronary insufficiency

A. Uncomplicated forms of recent myocardial infarction (thrombotic closure)

(*a*) Anterior

(*b*) Posterior

B. Complicated forms of recent myocardial infarction

1. Sclerotic closure

(*a*) Anterior

(*b*) Posterior

2. Combined anterior and posterior infarctions (one recent infarct)

(*a*) Old posterior and recent anterior

(*b*) Old anterior and recent posterior

3. Multiple recent small infarctions

II. Progressive or nonprogressive chronic coronary insufficiency (coronary sclerosis without infarction)

(*a*) Distinctive electrocardiogram resembling that with anterior infarction

(*b*) Distinctive electrocardiogram resembling that with posterior infarction

(*c*) Indeterminate electrocardiogram

III. Transitory (acute) coronary insufficiency

IV. Suddenly fatal coronary insufficiency (thrombosis, embolism, ventricular fibrillation)

A few words regarding each of these subdivisions are not amiss here. The uncomplicated forms of myocardial infarction consist of the classic types of coronary occlusion which our own and previous autopsy material shows to be due to sudden thrombotic closure (figs. 1 and 4 *A* and *C*).

Among the complicated forms of myocardial infarction are those due to the relatively less abrupt occlusion resulting from sclerotic plaques in the coronary arteries. Patients with this form of closure often go through periods of mild heart failure and die when some other complication, such as an operation or pulmonary, renal or cerebral involvement, is superimposed. The electrocardiograms are less characteristic, and lead IV is often more diagnostic than the standard three leads (figs. 2, 3 and 4 *D*). Another form of complicated myocardial infarction is that in which the presence of several infarcts confuses the electrocardiographic picture (figs. 5 to 7, 11 and 18); usually the changes resulting from the most recent infarct are those that dominate the curves. Another form is that in which multiple small infarcts are present

(fig. 8). Repeated infarction in the same area is another variety of this last subdivision; each occlusion results in changes in the ST segment of a similar type, which slowly disappear, only to reappear again with each new attack (fig. 17).

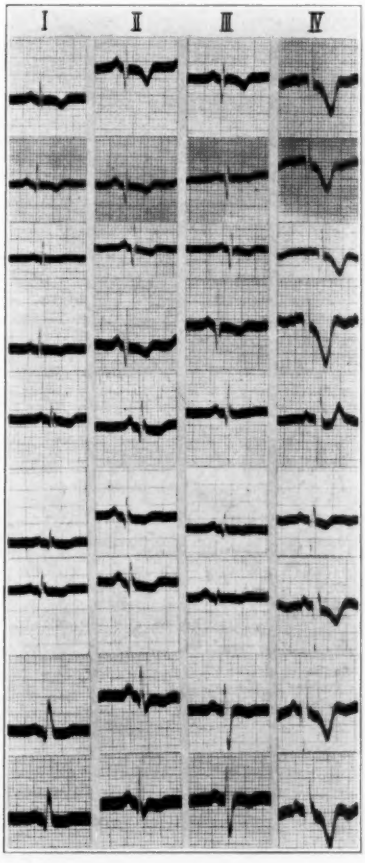

Fig. 18.—Serial electrocardiograms showing a late stage of atypical infarction of the posterior wall with a transitory change suggesting the superposition of infarction of the anterior wall, with recovery.

Attack	6/29/33	Attack	6/20/34
Curves taken	7/21/33	Curves taken	7/ 3/34
	8/17/33		8/ 9/34
	9/22/33		9/12/34
	1/24/34		1/18/35
			2/20/35
		Death (no autopsy)	6/ 6/35

In the group of cases of chronic coronary insufficiency, whether nonprogressive or progressive, which we have previously reported [1h] and to which we have now added 8 additional cases with autopsy data, some of the electrocardiograms resemble those encountered in cases of myocardial infarction (fig. 10), except that the serial curves do not follow the course typical of cases of healing infarction. Others in this group show abnormalities of a more indeterminate nature (fig. 9). There are a number of reports in the literature of similar cases.[27] It is possible that the presence of electrocardiographic changes resembling those seen in cases of recent infarction is evidence of localized ischemia while absence of such changes is evidence of more generalized ischemia. It appears that the electrocardiogram not only does not depict the fibrosis or even the infarction but depicts only the presence of localized or gen-

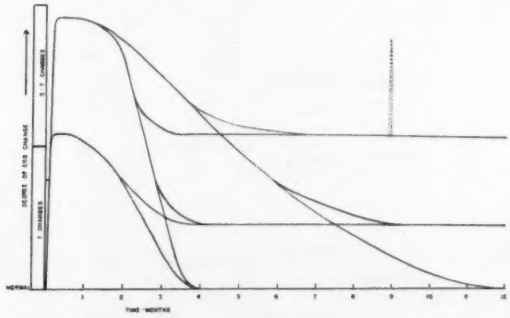

Fig. 19.—Diagram illustrating the possibilities of time events in a case of recent infarction as disclosed by serial electrocardiograms when at first there is little or no coronary insufficiency. The curves show (*a*) two degrees of severity of the attack, (*b*) two rates of recovery from the more severe attack, (*c*) complete and partial restoration and (*d*) (the dotted line) later superimposed acute transitory coronary insufficiency not giving rise to an infarct. When the patient starts with a certain degree of coronary insufficiency, as indicated by a short horizontal line half way up the upstroke, complete restitution will still leave an abnormal electrocardiogram.

eralized ischemia of the living muscle cells. This was the conclusion we came to in our previous study.[1h]

Transitory (acute) coronary insufficiency is another type of condition which is often noted in cases of coronary disease. It usually

27. Burton, J. A. K.; Cowan, J.; Kay, J. H.; Marshall, A. J.; Rennie, J. K.; Ramage, J. H., and Teacher, J. H.: Four Cases of Fibrosis of the Myocardium with Electrocardiographic and Post-Mortem Examination, Quart. J. Med. **23**:293, 1930. Levine and Brown.[71] Gilchrist and Ritchie.[7n] Nathanson.[7o]

occurs[28] as the result of excessive effort, an emotional crisis, very irregular or very rapid heart action or infarction of the kidneys, spleen or lungs, during congestive heart failure, or as the result of syphilitic involvement at the mouth of the coronary arteries. These conditions may produce transitory (acute) coronary insufficiency which does not result in permanent injury to the myocardium, although causing temporary electrocardiographic deformity and giving rise to such findings and symptoms as pulmonary edema, cardiac asthma, paroxysmal (nocturnal) dyspnea and angina pectoris. The occurrence of such changes in the electrocardiogram in the presence of these complications should make one seriously consider the transitory (acute) type of coronary insufficiency. The character of the electrocardiographic abnormalities associated with this condition will depend also on whether the process is diffuse or localized. Such transitory electrocardiographic changes again

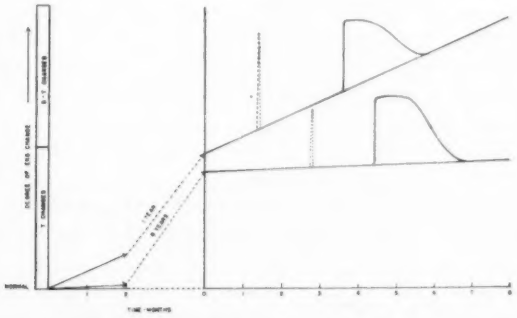

Fig. 20.—Diagram illustrating the difference in time course between so-called nonprogressive (lower curve) and progressive (upper curve) chronic coronary insufficiency. On each of these curves is shown a superimposed curve for transitory coronary insufficiency (dotted lines) and a superimposed curve for a subacute attack with infarction (solid lines).

28. Katz, L. N.; Hamburger, W. W., and Schutz, W. J.: The Effect of Generalized Anoxemia on the Electrocardiogram of Normal Subjects: Its Bearing on the Mechanism of Attacks of Angina Pectoris, Am. Heart J. **9**:771, 1934. Feil, H., and Siegel, M. L.: Electrocardiographic Changes During Attacks of Angina Pectoris, Am. J. M. Sc. **175**:255, 1928. Brow, G. R., and Holman, D. V.: Electrocardiographic Study During a Paroxysm of Angina Pectoris, Am. Heart J. **9**:259, 1933. Parkinson, John, and Bedford, D. E.: Electrocardiographic Changes During Brief Attacks of Angina Pectoris, Lancet **1**:15, 1931. Wood, F. C., and Wolferth, C. C.: Angina Pectoris: The Clinical and Electrocardiographic Phenomena of the Attack and Their Comparison with the Effects of Experimental Temporary Occlusion, Arch. Int. Med. **47**:339 (March) 1931. Hall, D.: Electrocardiograms of Two Patients During Attacks of Angina Pectoris, Lancet **1**:1254, 1932.

suggest that it is the ischemia of living muscle and not the presence of dead or scar tissue which causes the abnormalities observed with all forms of coronary insufficiency.

GENERAL SUMMARY AND CONCLUSION

We have reported on 200 cases of coronary occlusion studied for three years. We have made a careful detailed analysis of the incidence of various abnormalities in the standard three leads and the deviations of lead IV in cases of (*a*) recent anterior infarction, (*b*) recent posterior infarction and (*c*) combined anterior and posterior infarctions. The criteria for this division according to the type of infarction were based on the characteristic electrocardiographic deviations in our own and in other cases in which the diagnosis was verified at autopsy.

We have presented illustrations of the four lead electrocardiograms in 25 cases of recent infarction together with the pertinent autopsy data. Similar data are presented for 2 cases of recent small multiple infarcts and for 8 cases of coronary sclerosis without infarction. We have illustrated with actual serial curves and with diagrams the evolution of the classical changes in cases of recent anterior and posterior infarction due to thrombosis.

We have demonstrated the differences in the electrocardiogram in cases of recent infarction due to suddenly occurring coronary thrombosis and in cases of infarction due to slowly occluding sclerotic plaques.

We have, as a result of these studies, reached the following conclusions:

The incidence of all types of myocardial infarction due to coronary occlusion is greater in men than in women, and the incidence of anterior infarction is greater than that of posterior infarction.

The mortality from posterior infarction is relatively less than that from other types.

Septal involvement occurs with all types of myocardial infarction, but it is relatively more frequent with anterior infarction. If the septal infarction is near the apex, intraventricular block may not appear in the electrocardiogram.

Low "voltage" in the standard three leads occurs relatively more often with anterior infarction, but lead IV is usually not affected.

Preponderance of the left ventricle is most often associated with posterior infarction but may occur with anterior infarction.

Lead IV is of definite aid in the diagnosis of recent myocardial infarction due to coronary occlusion, especially anterior infarction.

The frequency of the various types of recent myocardial infarction is more in accord with autopsy statistics when four leads are used than when only the three limb leads are used.

Correlation with autopsy data shows:

(*a*) The classic forms of electrocardiographic variation, with early striking typical variations in the ST segment, are associated with recent infarction due to suddenly occurring thrombosis in a coronary artery.

(*b*) Atypical forms of electrocardiographic variations are in most cases associated with recent infarction due to slowly occluding sclerotic plaques, with extensive coronary sclerosis, but they are also seen (1) in cases in which a recent infarction is superimposed on an old one, (2) in the presence of recent multiple small infarcts or (3) in cases of recent infarction complicated by intraventricular block.

(*c*) In the absence of infarction, chronic coronary insufficiency due to coronary sclerosis may result in an electrocardiogram resembling that typical in cases of coronary occlusion or one possessing noncharacteristic abnormalities associated usually with a QRS_4 which is mainly or entirely upright. Serial curves will easily differentiate the former condition from a healing recent infarction.

(*d*) Transitory (acute) coronary insufficiency may produce electrocardiographic changes resembling those due to recent infarction without producing recognizable evidence of myocardial infarction post mortem. However, the rate of evolution in serial curves is different in the two conditions.

(*e*) Myocardial infarcts do heal and may not leave any clearly demonstrable anatomic evidence, and serial electrocardiograms are therefore vital in the demonstration of this recovery.

(*f*) In cases of chronic coronary insufficiency, progressive deviation from the normal in serial electrocardiograms is an unfavorable prognostic sign.

Charts are given to depict the time course with the different types of coronary insufficiency, and a series of idealized records is shown to depict the classic series of changes in leads I, III and IV in a typical case of recent anterior and a typical case of recent posterior myocardial infarction.

The manner of recording lead IV and the nomenclature to be used with respect to various kinds of chest leads are discussed.

The importance of basing the final diagnosis on the findings in all four leads and on changes in serial curves rather than on any special abnormality in any single record is emphasized.

NOTE.—The lead IV described in this report differs from the lead IV recently recommended by a special committee of the American Heart Association [29] as follows:

1. The precordial electrode in our studies is placed in the fourth interspace just to the left of the sternum, whereas for the standard lead

29. Standardization of Precordial Leads, J. A. M. A. **110**:395 (Jan. 29) 1938.

IV recommended by the American Heart Association's committee the precordial electrode is placed over the apex.

2. The electrodes in our studies are arranged so that relative positivity of the precordial electrode will cause a downward deflection, whereas according to the standard lead IV recommended by the American Heart Association's committee, the electrodes are arranged so that relative positivity of the precordial electrode gives an upward deflection.

The medical staff of Michael Reese Hospital gave us permission to study their patients and cooperated in the obtaining of follow-up data; Dr. O. Saphir, of the Department of Pathology, supplied the autopsy reports; Miss Phillips and Miss Bronson, electrocardiographic technicians, and several interns were of technical assistance, and Mrs. Salzman, social worker, assisted in obtaining the follow-up data for the clinic patients.

FEVER INDUCED BY THE INTRAVENOUS INJECTION OF TYPHOID-PARATYPHOID VACCINE

S. W. RANSON JR., M.D.
NEW YORK

Since vaccines of the typhoid group are administered intravenously in arthritis, iritis, thrombo-angiitis obliterans and other conditions and since there does not seem to have been any adequate study of the reaction caused by these vaccines, an inquiry into the more detailed nature of the normal response to the injection should serve a useful purpose. During a series of experiments designed to determine the effect of various hypothalamic lesions on the course of fever induced in cats by the intravenous injection of typhoid-paratyphoid vaccine, sixteen normal cats were studied.

Pinkston [1] recorded the inguinal temperature of twelve normal cats to which typhoid-paratyphoid vaccine had been administered intravenously. He made readings every 10 to 30 minutes "until the body temperature had started toward normal." Cannon and Pereira [2] described the temperature curves obtained for ten normal cats after intravenous or intramuscular injection of a suspension of dead typhoid bacilli. They did not state by what route the temperature was taken, nor did they describe the curves in any detail.

METHODS

Each cat was brought to the laboratory about 8 a. m., laid on its side on a specially designed canvas sling and secured in this position with canvas straps. It was thus securely but comfortably held.

The temperature was recorded in ink as a continuous curve by means of a Leeds and Northrup resistance temperature recorder, the resistance unit of which was inserted through the rectum and held securely in the colon at a constant distance of 14 cm. from the anus. A constant and deep placement of this unit was necessary because it was found that a temperature gradient exists in the cat's rectum between the outlet and a depth of from 8 to 10 cm. The resistance recorder was calibrated once a week against a United States Bureau of Standards thermometer in a constant temperature water bath. An area about

From the Institute of Neurology, Northwestern University Medical School, Chicago.

This study was aided by grants from the Rockefeller Foundation and the Committee on Scientific Research of the American Medical Association.

1. Pinkston, J. O.: Experimental Fever in Sympathectomized Animals, Am. J. Physiol. **111**:539 (April) 1935.

2. Cannon, W. B., and Pereira, J. R.: Increase of Adrenal Secretion in Fever, Proc. Nat. Acad. Sc. **10**:247, 1924.

3 or 4 cm. in diameter on the side of the cat's flank had been depilated the preceding day, and to this area a skin thermocouple was applied by means of a spring-mounted holder fastened to a ring-stand. The room temperature and humidity were recorded at frequent intervals from a wet and dry bulb thermometer, ventilated at about 3 meters per second by an electric fan.[3] All temperatures were recorded in degrees Fahrenheit.

In each case the animal was placed in the sling immediately on being brought to the room, and all the apparatus was mounted and placed in function. The temperature curve was then recorded until a definitely stabilized base line had been established. This precaution is of considerable importance; the process of stabilization may consume 2 or 3 hours. When the animal's temperature had been definitely stabilized, 0.35 cc. of typhoid-parathyphoid vaccine[4] per kilogram of body weight was injected into the saphenous vein. One uniform lot was used, all the vials having been filled at the same time from the same bottle of freshly prepared stock vaccine. The vaccine contained 1,000,000,000 killed typhoid, 750,000,000 killed paratyphoid alpha and 750,000,000 killed paratyphoid beta organisms in each cubic centimeter. The dosage was not varied at any time. Observations were made of the respiration and the skin temperature at frequent intervals (from 5 to 15 minutes) for 3 or 4 hours after the injection. It was not possible to make reliable observations on the pulse rate. About 5 p. m. the skin thermocouple was removed, the fan ventilating the wet bulb thermometer was stopped and the set-up was left otherwise undisturbed, so that a constant record of the animal's temperature was made until the termination of the experiment the next morning, about 20 hours after the injection.

RESULTS

Often immediately, almost always within from 10 to 30 minutes, after the injection the temperature began to rise, usually accompanied with or preceded by shivering. Generally the pupils were dilated, and the animal was excited and restless. On some occasions there appeared to be erection of hair. The skin thermocouple indicated cutaneous vasoconstriction. There was a moderate decrease in respiration. On an average of 48 minutes after injection of the vaccine the temperature reached a preliminary peak (hereafter called the first peak) at an average elevation of 1.2 F. above the base line (chart 1). Three of the normal animals showed no definite first peak. Shivering now ceased or, more usually, had been absent for from 10 to 15 minutes before the attainment of the first peak. The pupils narrowed; in nearly every case defecatory movements began,[5] usually with passage of considerable

3. The highest recorded room temperature was 83 F.; the lowest, 76 F.; the greatest variation during any one experiment, 2 F. The highest recorded relative humidity was 45 per cent; the lowest, 23 per cent; the greatest variation in relative humidity during any one experiment, 2 per cent.

4. The vaccine was furnished by the Abbott Laboratories.

5. It is realized that these movements were in part occasioned or exaggerated by the presence in the colon of the rectal resistance unit. Their significance lies in their constant temporal correlation with other events of a parasympathetic nature.

soft stool, occasionally with urination and, in the male, erection of the penis. Respiration was accelerated, and on three occasions the animal panted for from 5 to 15 seconds. The skin thermocouple indicated cutaneous vasodilatation. The rectal temperature fell away rapidly from the first peak to an average intermediate low point 0.6 F. below the base line, reached on an average of 114 minutes after the injection. Only one animal showed no such definite intermediate fall. Shortly before the low point of this intermediate fall was reached, the animal usually began to shiver, the pupils dilated and respiration became slower. The skin thermocouple indicated cutaneous vasoconstriction. In the train of these symptoms the temperature again began to rise, not so steeply as during the first rise, but more sustainedly, attaining a peak (hereafter called the second peak), averaging 1.8 F. above the base line, at an average of 279 minutes after the injection. Four of the

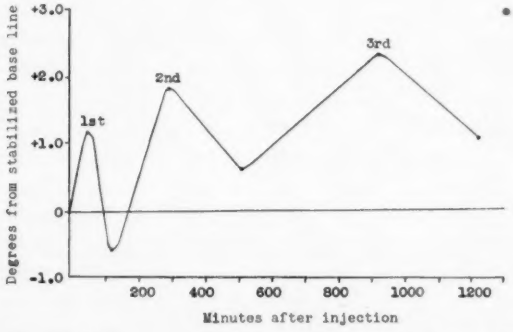

Chart 1.—Composite temperature curve for sixteen normal cats after injection of typhoid-paratyphoid vaccine intravenously. On the ordinate is plotted the body temperature in degrees Fahrenheit above or below the stabilized preinjection temperature. Time in minutes is represented on the abscissa.

sixteen animals showed no well marked second peak. The temperature fell away from the second peak slowly and irregularly, with minor ups and downs, to reach, on the average, a second intermediate low point, 0.57 F. above the base line, 506 minutes after the injection. Then began a slow and irregular rise toward a third peak, which, on the average, reached 2.3 F. above the base line 922 minutes after the injection. Thereafter the temperature fell slowly and irregularly. The next morning the temperature still averaged 1.06 F. above the base line. Only two animals failed to show a reasonably well defined second intermediate fall and a third peak. Chart 2 shows a fairly typical temperature curve for a normal cat, but the fall after the first peak was smaller than usual.

One of the sixteen normal cats (experiment 22) responded to the injection in a peculiar manner. During the first 45 minutes after the injection the temperature remained practically constant, although the cat shivered once or twice. Thereafter the rectal temperature fell rapidly to a low point, 2.3 F. below the base line, 209 minutes after the injection. From this point it rose, accompanied with some shivering, to a peak, 0.8 F. below the base line, 378 minutes after the injection. After a minor recession from this peak it rose to a third peak, 0.4 F. above the base line, 1,121 minutes after the injection. It fell away slowly from this point, until at the conclusion of the experiment, 1,275 minutes after the injection, the temperature was exactly at the base line. This cat was apparently perfectly normal and healthy. There had been no alteration in the conditions of the experiment.

The average respiratory rate of the stabilized animals just before the injection was 50.7 per minute. The average highest rate in the period between injection and attainment of the first peak was 46; the

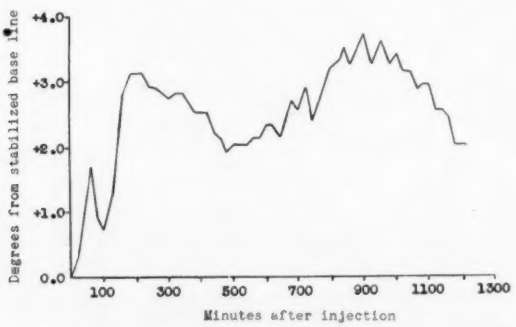

Chart 2.—Typical temperature curve for the normal cat (experiment 25) after injection of typhoid-paratyphoid vaccine intravenously.

average lowest rate for this period, 42.8. The average highest rate for the period between the first peak and the trough of the intermediate fall was 92.7; the average lowest rate for this period, 48. Three animals panted for from 5 to 15 seconds during this period, but the respiratory rate during panting, being of such short duration, was not entered on the charts or averaged into the respiratory rates of this period. Hence the averages are not unduly weighted by these occurrences. In the period of rising temperature between the trough of the intermediate fall and the second peak, the average maximum respiratory rate was 41.1 and the average minimum rate 33.1 per minute. There was thus some slowing of respiratory rate during the first rise, considerable acceleration during the intermediate fall and a return to a slow respiratory rate in the phase of the second rise.

All but two of the sixteen animals shivered during one or the other of the two phases of rising temperature. Nine shivered during the first rise; ten, during the second rise.

The readings for the skin thermocouple were, of course, not readings of true cutaneous temperature. Owing to the method of application of the thermocouple, there was present an unevaluated element of deep temperature, which would increase the reading of the skin thermocouple during a period of rising general body temperature and would therefore decrease the apparent amount of cutaneous vasoconstriction; during a period of falling general body temperature it would decrease the reading of the skin thermocouple and therefore would decrease the apparent amount of cutaneous vasodilatation. It is obvious, however, that if cutaneous vasoconstriction is indicated during a rise or fall in body temperature, it is undoubtedly present, although not accurately measured.

All but one of the thirteen animals that showed a definite first peak showed cutaneous vasoconstriction during that period, as judged by failure of the reading for the skin thermocouple to rise by the same amount as the rectal temperature. This lag averaged 0.4 F. All but two of the fifteen animals that exhibited a definite intermediate fall showed cutaneous vasodilatation, averaging 0.4 F., as calculated by this method. Six of the eight animals exhibiting a definite second peak, and for which the data were complete, showed cutaneous vasoconstriction, as judged by this method, the average being 0.3 F.

COMPARISON WITH THE RESULTS OF OTHER INVESTIGATORS

Cannon and Pereira [2] and Pinkston [1] described normal temperature curves after the injection of typhoid and of typhoid-paratyphoid vaccine, respectively. Cannon and Pereira administered the vaccine either intramuscularly or intravenously and did not give any of the details of their experiment, i. e., method of taking temperature, method of stabilizing temperature before injection, dose of vaccine and interval between individual observations of temperature. Pinkston took the temperature inguinally instead of rectally; observations were spaced at intervals of from 10 to 30 minutes. He assumed stabilization of the preinjection body temperature after the animal had been in the laboratory 1 hour.

Both papers described first and second peaks, with an intermediate fall. Neither paper described a third peak, since both groups of experimenters apparently terminated their observations after the attainment of the second peak. Cannon and Pereira stated that the second peak may exceed the first; Pinkston stated that the first peak usually exceeds the second. I found that the second peak was almost always higher than the first; in contrast again to Pinkston's results, I found that in the fall from the first peak the temperature usually returned to the base line or below. I believe that the discrepancies between my results

and those of Pinkston may well be due to the errors which were inherent in his method of taking the temperature, i. e., inguinally; that method of observation is complicated by components of cutaneous vasoconstriction and vasodilatation. Cannon and Pereira found shivering in the first rise, but not in the second. I found it actually more common in the second than in the first. Cannon and Pereira mentioned the signs of sympathetic stimulation during the rise toward the first peak, and these were also briefly touched on by Pinkston. Neither paper mentioned parasympathetic symptoms during the period of falling temperature.

CONTROL EXPERIMENTS

In order to determine what range of variation in temperature might be expected in the cat merely as the result of the normal diurnal variation, together with the manipulation to which the animals were subjected during these experiments, two normal cats were carried through exactly the same procedure as were the main series of sixteen cats, except that instead of typhoid-paratyphoid vaccine an equal volume of sterile physiologic solution of sodium chloride was injected intravenously. The first of these control animals showed a highest upward variation from the stabilized base line of 0.9 F. The lowest downward variation from the base line was 0.2 F. The second cat showed a highest upward variation from the base line of 0.3 F. The lowest downward variation was 0.7 F.

The range of total variation was 1.1 F. for the first cat and 1 F. for the second cat. This corresponds well with the normal diurnal variation of temperature in the cat reported by Pinkston as from 0.9 to 1.8 F. It is apparent that the manipulations of the experiment had little if any effect.

To make certain that the effects described in the main body of the experiment were not merely those of a particular brand or shipment of typhoid-paratyphoid vaccine and, further, to make certain that they were not properties of a mixed vaccine that would not be found in a vaccine prepared from typhoid bacilli alone, a sample of unmixed typhoid vaccine was obtained from the Chicago Board of Health. A dose of this vaccine, which contained a number of organisms equal to that used in the main experiment on the series of sixteen cats, was injected intravenously into each of two normal cats. The resultant temperature curves and other observations differed in no essential detail from the norms established by the other experiments. The detailed data will not be given.

Effects of Ether.—In addition, five normal animals were anesthetized as a preliminary with ether by inhalation for about 10 minutes. While each animal was in a stage of light surgical anesthesia, the usual dose of typhoid-parathyphoid vaccine was injected intravenously, and the anesthetic was at once discontinued. All other conditions were similar to those in the typical experiments. After the injection two of the animals showed an almost immediate fall in temperature, accompanied with pupillary constriction, excessive salivation, marked defecatory movements and marked and persistent panting. The temperature of one of the animals dropped 5.9 F. and that of the other 4.2 F. The experiment on the first animal was terminated the same day; the second was followed for 20 hours, and at the end of that time the temperature was still 4.2 F. below the base line. In the other three animals the first peak was lowered or absent, and panting, salivation, defecation and pupillary constriction were marked. Eventually, however, the temperature rose to a point well above the base line (4.3, 4 and 3.2 F., respectively).

COMMENT

The normal process of conservation of bodily heat apparently entails, among other mechanisms, mass sympathetic stimulation. Cannon and Querido [6] demonstrated that an animal with a denervated heart shows marked acceleration in cardiac rate when exposed to cold; this they said is indicative of increased secretion of epinephrine. According to Aub, Bright and Forman,[7] McIver and Bright [8] and Cori and Buchwald,[9] the liberation of epinephrine increases the oxidative processes of the body. Sympathectomized animals are more susceptible to cold than are normal animals, and they lose their body heat more rapidly when exposed to it (Cannon, Newton, Bright, Menkin and Moore; [10] Sawyer and Schlossberg [11]).

H. H. Meyer [12] advanced the theory that the mechanism for regulation of body temperature includes two centers; one of which, promoting increases in temperature, gives rise to generalized sympathetic reactions, and the other, promoting decreases in temperature, causes generalized parasympathetic reactions. Phenomena present in normal cats during the phases of rising temperature (excitement, dilatation of the pupils, cutaneous vasoconstriction and occasionally erection of hair) suggest a state of generalized sympathetic stimulation. Similarly, those phenomena which accompany the phases of falling temperature (pupillary constriction, cutaneous vasodilatation and defecation and occasionally urination and penile erection) suggest a period of generalized parasympathetic stimulation.

It is well known that drugs which stimulate the sympathetic system, such as epinephrine, tyramine hydrochloride, and other amines, ephedrine and especially betatetrahydronaphthylamine, all produce fever if given in sufficient doses. Pinkston [1] found that completely sympathectomized

6. Cannon, W. B., and Querido, A.: The Rôle of Adrenal Secretion in the Chemical Control of Body Temperature, Proc. Nat. Acad. Sc. **10**:245, 1924.

7. Aub, J. C.; Bright, E. M., and Forman, J.: The Metabolic Effect of Adrenalectomy upon the Urethanized Cat, Am. J. Physiol. **61**:349 (July) 1922.

8. McIver, M. A., and Bright, E. M.: Changes in Metabolism Following Adrenal Stimulation, Am. J. Physiol. **68**:622 (May) 1924.

9. Cori, C. F., and Buchwald, K. W.: The Calorigenic Action of Epinephrine in Frogs Before and After Hepatectomy, J. Biol. Chem. **92**:367 (July) 1931.

10. Cannon, W. B.; Newton, H. F.; Bright, E. M.; Menkin, V., and Moore, R. M.: Some Aspects of the Physiology of Animals Surviving Complete Exclusion of Sympathetic Nerve Impulses, Am. J. Physiol. **89**:84 (June) 1929.

11. Sawyer, M. E. M., and Schlossberg, T.: Studies of Homeostasis in Normal, Sympathectomized and Ergotaminized Animals: I. The Effect of High and Low Temperatures, Am. J. Physiol. **104**:172 (April) 1933.

12. Meyer, H. H.: Theorie des Fiebers und seiner Behandlung, Verhandl. d. deutsch. Kong. f. inn. med. **30**:15, 1913.

animals to which typhoid-paratyphoid vaccine was administered intravenously displayed a slow rise to a late and low maximum temperature, with an absence of conspicuous peaks. Animals subjected to the same type of injection, in which only the splanchnic sympathetic outflow was intact, showed a similar response, although the maximal temperature occurred earlier and distinct peaks were more common. Cannon and Pereira [2] found that the first temperature peak induced in normal animals by the injection of typhoid vaccine did not occur after inactivation of the adrenal glands. Pinkston, on the other hand, found that when the only lesion of the sympathetic nervous system was inactivation of the adrenal glands there were usually two distinct temperature peaks. In these animals the speed of attainment of maximal fever was almost, but not quite, that of normal animals.

G. E. Brown and his associates,[13] wishing to determine the amount of vasodilatation available in an extremity affected by thrombo-angiitis obliterans, followed the simultaneous courses of oral and cutaneous temperatures after the injection of typhoid vaccine intravenously into patients afflicted with this disease. During the course of the ensuing chill (period of rising general body temperature) there was a marked fall in the cutaneous temperature of the extremity. At, or just before, the peak of this rise there was tremendous vasodilatation, and the cutaneous temperature of the extremity rose well above the base line originally established. The absolute rise in cutaneous temperature was much greater than the absolute rise in oral temperature. Accompanied with this vasodilatation, the oral temperature fell away from the peak. (The authors did not follow the course of events beyond this point.) Thus, in the human being, as in normal cats, the period of rising temperature is accompanied with vasoconstriction; the period of falling temperature, by vasodilatation.

Pinkston [14] noted prompt vasoconstriction, with a fall in cutaneous temperature, in the ear of the normal rabbit after injection of typhoid-paratyphoid vaccine. This appeared within a short time (5 to 10 minutes) after the injection and persisted until the peak of the temperature had been reached, to be replaced suddenly by a rise in cutaneous temperature (vasodilatation). The body temperature then fell. The course of events was not followed beyond this point. There was some vasoconstriction (but only in 50 per cent of the cases) in the sympathectomized ear. Inactivation of the adrenal glands appeared to do away

13. Brown, G. E.; Allen, E. V., and Mahorner, H. R.: Thrombo-Angiitis Obliterans, Philadelphia, W. B. Saunders Company, 1928, p. 182. Brown, G. E.: Thrombo-Angiitis Obliterans, Surg., Gynec. & Obst. **58**:297 (Feb.) 1934.

14. Pinkston, J. O.: Peripheral Circulation During Experimental Fever, Am. J. Physiol. **110**:448 (Dec.) 1934.

with the early vasoconstriction in the sympathectomized ear, but had no effect on the delayed vasoconstriction (that appearing after from 1 to 3 hours).

Hewlett [15] studied the rate of blood flow in the periphery in several cases of abrupt febrile rises due to sepsis in the human being. There was a decrease in the rate of flow during the period of rising temperature. When the temperature reached its peak there was a marked increase in flow, exceeding the original rate of flow and persisting on into the period of falling temperature.

Fremont-Smith, Morrison and Makepeace [16] made direct microscopic observations of the capillaries of the human nail fold during the febrile reaction produced by the injection of typhoid vaccine. They found that, coincident with the onset of the fever, complete capillary stasis occurred rapidly, the stasis continuing until the temperature had nearly reached its height. Just before the height of the temperature was reached the flow of blood again began in the capillaries, rapidly reaching a more than normal rapidity. Capillary pulsation set in. The temperature simultaneously began to fall. The rapid flow lasted throughout the period of falling temperature. The authors said that they believed that the stasis during the period of rising temperature is due to constriction of the terminal arterioles.

To summarize: The febrile process induced by the intravenous injection of typhoid-paratyphoid vaccine seems to consist of alternate stimulation of the mechanism for conservation of bodily heat, *including the sympathetic system,* and then of the mechanism for loss of bodily heat, *including the parasympathetic system.* Probably the two antagonistic mechanisms are stimulated simultaneously, first one and then the other predominating. The cycle of these alternate reactions is apparently repeated at least several times, and the algebraic result in the normal animal when this particular bacterial protein is used is a period of many hours in which the body temperature, although rising and falling in cycles, is maintained at some distance above the base line.

Not all vaccines when injected into animals cause sustained fever. Pfeiffer [17] showed that chloroform-killed cholera vaccines when injected intraperitoneally drove the animal's temperature down to 33 C., with signs of collapse. After small doses there was merely a slight rise in

15. Hewlett, A. W.: The Effect of Room Temperature upon the Blood-Flow in the Arm, with a Few Observations on the Effect of Fever, Heart **2**:230, 1911.

16. Fremont-Smith, F.; Morrison, L. R., and Makepeace, A. W.: Capillary Blood Flow in Man During Fever, J. Clin. Investigation **7**:489 (Aug.) 1929.

17. Pfeiffer, R.: Untersuchungen über das Choleragift, Ztschr. f. Hyg. u. Infektionskr. **11**:393, 1892. Pfeiffer, R., and Wassermann, A.: Untersuchungen über das Wesen der Choleraimmunität, ibid. **14**:46, 1893. Pfeiffer, R.: Studien zur Choleraätiologie, ibid. **16**:268, 1894.

temperature. After larger doses there was a slight rise in temperature; then in 2 or 3 hours, marked hypothermia. Novy, De Kruif and Novy,[18] among others, stated that when autolyzed suspensions of Trypanosoma surra, nagana and others are injected there occur "marked toxic effects," with hypothermia.

One is tempted to assume that various bacterial proteins may differ in their proportionate effects on the mechanisms of heat preservation and heat loss and that the algebraic summation of the cyclic action of these mechanisms results in hyperthermia in the normal animal with the usual bacterial proteins, but causes hypothermia in the normal animal when cholera and trypanosome vaccines are used.

Further, it may be assumed that if the mechanism of heat preservation or of heat loss or the mechanism coordinating them is abnormal, injection of the usual bacterial proteins may produce hypothermia in animals possessing the abnormal mechanism, although the protein injected is one that ordinarily produces a hyperthermic response. Thus, mere preliminary etherization of the animal for from 5 to 10 minutes is often sufficient to render its response so abnormal that hypothermia results from the injection of typhoid-paratyphoid vaccine, in spite of the fact that etherization of that duration will not of itself produce any noteworthy fall in temperature. Much more striking were the results obtained by injection of typhoid-paratyphoid vaccine intravenously into cats with certain hypothalamic lesions. The cats responded in a cyclic manner, but the falls in temperature much exceeded in magnitude the rises, the final algebraic result being sustained and tremendous hypothermia (5 to 11 F.). (These results will be published in detail in a separate paper.)

The infrequent fatal and near fatal reactions which have occurred as a result of the injection of typhoid vaccine by the various routes have not been adequately described or explained. Reported during these reactions have been dyspnea and cyanosis (Nichols and Hitchens[19]); vomiting and marked fall in blood pressure (Scully[20]), and dyspnea, cyanosis and dilatation of the heart (Hale and Hartman[21]). In none of these cases were records of the temperature made until there was marked improvement in the patient's condition. Some of these violent reactions are reminiscent of the parasympathetic symptoms attendant on the

18. Novy, F. G.; De Kruif, P. H., and Novy, R. L.: Anaphylatoxin and Anaphylaxis, J. Infect. Dis. **20**:499, 535, 566, 589, 618, 629, 657 and 776, 1917.

19. Nichols, H. J., and Hitchens, A. P.: The Reactions of Typhoid Vaccination, J. Lab. & Clin. Med. **11**:517 (March) 1926.

20. Scully, F. J.: The Reactions After Intravenous Injections of Foreign Protein, J. A. M. A. **69**:20 (July 7) 1917.

21. Hale, G. D., and Hartman, F. W.: The Dangers of Intravenous Injection of Anti-Typhoid Vaccine, U. S. Nav. M. Bull. **12**:1 (Jan.) 1918.

phases of falling temperature in the cats in the experiments reported here, especially in the abnormal animals in which hypothermic and parasympathetic reactions predominated.

There seems to be general agreement that epinephrine is the treatment of choice in these accidents and that its administration is actually followed by amelioration of the symptoms (Nichols and Hitchens [19] and Hench [22]). Hench also mentioned the use of atropine in these situations. The reactions have been regarded by many as expressions of anaphylaxis (among others, Hale and Hartman [21] and Nichols and Hitchens [19]), but this view is by no means universally held (Miller [23]).

From 1914 to 1920 there was considerable interest in the treatment of typhoid by the intravenous injection of typhoid vaccine. The results were striking. From half an hour to an hour after the injection there occurred a chill, lasting for from 10 to 20 minutes, the temperature rising to 40 or 41 C. and then *falling sharply to normal or well below*, usually with marked sweating, often nausea and vomiting, and profuse liquid diarrhea in cases in which constipation had previously been present (among others may be cited Leschke,[24] Sladek and Kotlowski,[25] Eggerth,[26] Kraus [27] and Von Adelung [28]). That this striking temperature reaction was not anaphylactic was shown by Kraus,[29] for intravenous injection of Bacillus coli vaccine in cases of typhoid produced similar results in his experience. Indeed, so did intravenous injections of deutero-albumose (Lüdke [30]). It may be assumed in the light of the foregoing discussion that the injection of vaccine intravenously into patients with typhoid produces, after a preliminary rise in temperature, with predominance of the heat retention mechanism and sympathetic

22. Hench, P. S.: Usual and Unusual Reactions to Protein (Fever) Therapy, Arch. Int. Med. **49**:1 (Jan.) 1932.

23. Miller, J. L.: The Non-Specific Character of Vaccine Therapy, J. A. M. A. **69**:765 (Sept. 8) 1917.

24. Leschke, E.: Erfahrungen über die Behandlung der Kriegsseuchen, Berl. klin. Wchnschr. **52**:634, 1915.

25. Sladek, J., and Kotlowski, S.: Zur Vakzinetherapie des Typhus abdominalis, Wien. klin. Wchnschr. **28**:389, 1915.

26. Eggerth, H.: Ueber die Behandlung des Typhus abdominalis mit Typhusvakzine, Wien. klin. Wchnschr. **28**:209, 1915.

27. Kraus, R.: Bemerkungen über Schutzimpfungen und eine Bakteriotherapie des Typhus abdominalis, Wien. klin. Wchnschr. **27**:1443 (Nov.) 1914.

28. Von Adelung, E.: Vaccine Treatment of Typhoid, California State J. Med. **18**:175 (May) 1920.

29. Kraus, R.: Zur Frage der Vakzinetherapie des Typhus abdominalis, Deutsche med. Wchnschr. **40**:1556, 1914.

30. Lüdke, H.: Die Behandlung des Abdominaltyphus mit intravenösen Injektionen von Albumosen, München. med. Wchnschr. **62**:321 (March) 1915.

stimulation, the usual cyclic shift to predominance of the heat loss mechanism, with parasympathetic signs; but this phase of the cycle, for reasons which are not obvious, is markedly exaggerated and prolonged.

SUMMARY

Typhoid-paratyphoid vaccine was injected intravenously into sixteen normal cats. The resultant temperature curves were recorded continuously for 20 hours. The reaction in the normal cat to the injection of typhoid-paratyphoid vaccine intravenously, which is described in detail, consists essentially of cyclic stimulation, first of the heat elaboration mechanism, with sympathetic signs, and then of the heat loss mechanism, with parasympathetic signs. The heat preservation mechanism predominates, so that the algebraic result is hyperthermia of a sustained nature. There are usually three temperature peaks, the third one being higher than the second and the second being higher than the first.

When the mechanism of heat preservation or of heat loss, or the mechanism coordinating them, is abnormal, the reaction to the injection of the vaccine may be one in which the heat loss mechanism, with parasympathetic signs, predominates, and the algebraic result may be marked and sustained *hypothermia,* although the bacterial protein is one which ordinarily produces hyperthemia. This abnormality of the mechanism of the animal which has been given an injection of vaccine may result from preliminary etherization or from localized lesions of the hypothalamus.

Certain bacterial proteins apparently differ from the usual bacterial proteins in that when injected into the *normal* animal they produce a cyclic response in which the heat loss mechanism, with parasympathetic signs, predominates, and the result is sustained and marked *hypothermia.*

Violent clinical reactions to the injection of typhoid vaccine and the remarkable thermolytic response which have been obtained by the intravenous injection of typhoid vaccine during the course of typhoid are considered in the light of the preceding discussion.

Progress in Internal Medicine

DISEASES OF METABOLISM AND NUTRITION

REVIEW OF CERTAIN RECENT CONTRIBUTIONS

RUSSELL M. WILDER, M.D., PH.D.
ROCHESTER, MINN.
AND
DWIGHT L. WILBUR, M.D.
SAN FRANCISCO

I. DISEASES OF METABOLISM

By Dr. Wilder

DISORDERS OF FAT METABOLISM

Cholesterol Metabolism.—Drs. Thannhauser and Magendantz [1] have given me permission to include in this section the following review of a paper of theirs to be published in the near future. Dr. Thannhauser and his associates are recognized as outstanding authorites on cholesterol metabolism, a subject which only recently, and to a great extent through their efforts, has become somewhat understandable. It now is well established that the nucleus of the sterols can be manufactured in the body, although it remains not definitely known in what cells or organs this synthesis is accomplished. It is suspected that it is accomplished in the liver; at least the value for cholesterol in the blood is lowered by hepatectomy. Nor is there knowledge as yet as to what raw material serves as the source of the sterol skeleton, other than that certain yeasts are able to make ergosterol from various sugars—best from polysaccharides. Balance experiments with cholesterol are of little help in deciding whether the ring system of cholesterol can be disrupted in intermediary metabolism, for the reason that excretion occurs into the bowel and destruction of cholesterol can be effected there by bacteria. Disintegration products of the sterols, in which the sterol ring skeleton is broken up, have not been found in the blood or tissues, although derivatives dependent on changes in the side chain, like the sex hormones, are well known.

From the Division of Medicine, the Mayo Clinic (Dr. Wilder), and the Stanford University School of Medicine (Dr. Wilbur).

1. Thannhauser, S. J., and Magendantz, H.: The Different Clinical Groups of Xanthomatous Diseases: A Clinical Physiological Study of Twenty-Two Cases, to be published.

The esterification of cholesterol occurs in the liver, if one may judge from the fact that that part of the value for the total cholesterol of the blood attributable to cholesterol esters frequently is diminished in disease of the parenchyma of the liver. Reduction (hydrogenation!) to dihydrocholesterol can occur, as was reported by Schoenheimer and Hrdina,[2] who demonstrated dihydrocholesterol in the serum and tissues of normal men and increased amounts of it in the serum and tissues of a patient with xanthomatosis. However, the bile acids, which it was supposed might be derived from a stereo-isomer of dihydrocholesterol and thus from the sterols of the food, apparently are not so derived but originate by synthesis in the liver. It was found by Schoenheimer and his co-workers that when deuterium was attached to the double bond of cholesterol and this deuterium cholesterol was fed to animals, the bile acids afterward contained no deuterium.

The ability of the intestine to excrete cholesterol varies with the species; in man, according to Schoenheimer, there is variability with the individual. Herbivorous animals, while capable of absorbing it, cannot excrete it, which may explain the ease with which hypercholesteremia, with consequent atheromatosis, is obtained by feeding cholesterol to rabbits. The phytosterols of plants are not absorbed by either herbivores or carnivores; the possibility of favorably affecting conditions of hypercholesteremia in man by omitting animal fats from the diet was suggested thereby.

An important function of cholesterol is indicated "by the fact that cholesterol and cholesterol esters are present in a constant percentage in every lipid mixture occurring on the surface or within the cell."[3] Cholesterol is a hydrophobic colloid and thus plays a part in the exchange not only of fat-soluble material but also of fluid. The presence in the tissues of dihydrocholesterol suggested to Thannhauser and Magendantz another function—a role in an oxidation-reduction system (cholesterol $\rightleftarrows$ dihydrocholesterol).

Hypercholesteremia may be taken to indicate that the excretion of cholesterol is not in pace with the supply, whether endogenous or exogenous. Its occurrence usually is associated with that of cells filled with lipids, called foam cells or xanthoma cells. Such cells are found in widely scattered nests in various organs or accumulated in tumorous masses, called xanthomas, in the skin and other tissues. However, as

2. Schoenheimer and Hrdina, cited by Thannhauser and Magendantz.[1]

3. I am not familiar with the evidence which supports this statement. The percentage of total lipid represented by cholesterol and cholesterol esters, as determined by chemical analyses of blood and xanthoma tissue, varies greatly (see Montgomery and Osterberg [4]).

Thannhauser and Magendantz have related, conditions in which foam cells and xanthomas occur are not always dependent on an excess in the blood of cholesterol or other lipids.

Xanthomatosis.—The xanthomatoses have been classified by Thannhauser and Magendantz as primary and secondary. The secondary type they have attributed to hyperlipemia. Characteristic of it is the "eruptive" xanthomatosis of diabetes. The primary type they have subdivided into conditions characterized by elevated values for blood cholesterol and conditions characterized by normal values for the cholesterol and other lipids of the blood. The occurrence of xanthomatosis without hyperlipemia led them to depart from the view of Pick, that the xanthoma cell is simply a reticular cell overloaded with lipids as a result of hyperlipemia depending on some (unestablished) extracellular general disturbance of fat metabolism, and to suggest that the disturbance in question is intracellular and limited to certain reticular cells. They concluded that in those cases in which they classified the condition as primary or essential xanthomatosis, the xanthoma cells themselves form the doubly refractile substance they contain. They have pointed to analogies in other diseases of lipid metabolism as follows: In Gaucher's disease similar foam cells contain cerebrosides, whereas the blood contains only traces of cerebrosides. Likewise, in Niemann-Pick disease the content of the foam cells consists of diaminophosphatides (sphyngomyelins), whereas the values of the blood serum for mono-aminophosphatides and diaminophosphatides are normal or even lower than normal. Further to emphasize this point of view, Thannhauser and Magendantz have suggested the term metaplastic reticular cholesterosis for essential xanthomatosis, metaplastic reticular cerebrosidosis for Gaucher's disease and metaplastic reticular sphyngomyelinosis for Niemann-Pick disease.

Primary xanthomatosis, "a systemic disease," may be complicated by an eruptive xanthomatosis secondary to hyperlipemia. The eruptive form is a symptom of lipemia, and, in addition to occurring in diabetic lipemia, may be seen in other states of hyperlipemia, such as xanthomatous biliary cirrhosis, wherein lipemia is produced and eruptive xanthomas are added to those previously existent.

The two types of primary or essential xanthomatosis, that with and that without hypercholesteremia, differ in other characteristics. In type A the lesion of the skin is either the xanthoma planum or the xanthoma tuberosum; with it occur xanthomas of the tendons and tendon sheaths, of the blood vessels and of the walls of the bile ducts (with secondary biliary cirrhosis). In type B (without hypercholesteremia) the lesion of the skin is the xanthoma disseminatum; the pituitary body and the brain may be involved, and xanthomatous nodules may form in the membranous bones and in the orbit, provoking the

Hand-Schüller-Christian syndrome. However, other bones, including the long bones, may be affected and also the lungs and the pleura. The two types of primary xanthomatosis are not rigidly distinct, as is indicated by the necessity for adding a "combined type" to the classification. Thannhauser and Magendantz have classified the condition in 3 cases reported in the literature as of this combined type.

Another extensive discussion of xanthomatosis is contained in a paper by Montgomery and Osterberg,[4] whose comments likewise have been based on a study of a large number of cases. The most common form of cutaneous xanthoma, known as xanthoma tuberosum, was found almost invariably to be associated with an increase in the values for all the lipids of the blood, including cholesterol, of from two to five times the normal values. Also associated in a high percentage of cases was evidence of atheromatous lesions of the arteries. Thus, in 6 cases the clinical findings suggested the presence of coronary sclerosis; in 3 additional cases intermittent claudication was observed, and in 3 more there was other evidence of severe cardiovascular involvement. Three of the 4 patients with intermittent claudication (none of whom were Jews) and 3 of the patients with evidence of coronary sclerosis were women, which fact, combined with the early age of these patients—46 years—suggests that this form of atherosclerosis differs in etiology from the more common types of atherosclerosis and arteriosclerosis. Forty-six per cent of the group of 26 patients with xanthoma tuberosum had severe cardiovascular disease. Barker,[5] in 2 of these cases, made special studies and convinced himself of the presence of severe occlusive arterial disease. The values for blood cholesterol exceeded 600 mg. per hundred cubic centimeters, which is more than double the highest value for cholesterol found by him in a series of cases of the usual form of arteriosclerosis obliterans.

Disseminate xanthomatosis, represented by 4 of the cases of Montgomery and Osterberg, is characterized by multiple fine papular lesions of the skin of the flexural surfaces of the arms and frequently of the face. The mouth, pharynx and larynx also may be involved. Laryngeal obstruction necessitated tracheotomy in 2 of these cases. Mild diabetes insipidus also was present in 3 cases, and in 1 deposits of foam cells and deposits of cholesterol were seen at necropsy in the hypophysis and tuber cinereum. In contrast to the values in cases of xanthoma tubero-

4. Montgomery, Hamilton, and Osterberg, A. E.: Xanthomatosis: Correlation of Clinical Histopathologic and Chemical Studies of Cutaneous Xanthoma, Arch. Dermat. & Syph., to be published; Xanthomatosis: A Systemic Disease, Proc. Staff Meet., Mayo Clin. **12**:641-644 (Oct. 13) 1937.

5. Barker, N. W.: Occlusive Arterial Disease of the Lower Extremities Associated with Lipemia and Xanthoma Tuberosum, paper read before the Central Society for Clinical Research, Chicago, Nov. 5, 1937.

sum, the values for the lipids in the serum were normal or subnormal. In many of the cases of xanthoma tuberosum the hyperlipemia could be corrected, and partial or complete involution of the cutaneous lesions could be effected by means of a diet low in fat or free from cholesterol (free from animal fat). In contrast, in the cases of disseminate xanthomatosis the cutaneous lesions could not be influenced by these dietary procedures. On the other hand, the histologic appearance of the tuberous and that of the disseminate form of xanthoma were identical, revealing numerous foam cells and so-called Touton giant cells laden with lipids; the chemical analysis of lesions of both types revealed a "definite proportionate increase in the cholesterol content, reaching as high as 64 per cent of the total lipids and dropping to 18 per cent only in one old fibrous nodule which histologically revealed very few foam cells." This cholesterol content is much greater than that found in normal epidermis, and in 6 of 7 cases it exceeded the normal percentage ratio found for the lipids of the blood.

The lesion of the skin of the eyelids known as xanthelasma commonly has been regarded as having no serious significance. That this opinion may be erroneous and that xanthoma palpebrarum also may represent a metabolic disease were suggested. This condition frequently was seen in association with other forms of xanthoma of the skin; the histologic picture was found to be similar to that of other forms of xanthoma, and even in cases in which the only lesion of the skin was xanthelasma the values for serum lipids frequently were abnormally high.

Montgomery and Osterberg stated that they did not share Thannhauser's opinion that the cholesterol in the xanthoma is produced in situ. They said it did not seem logical to them to explain the hyperlipemia and hypercholesteremia in cases of xanthoma tuberosum by the production of lipids in the relatively few cutaneous nodules seen; and while the absence of increased values for blood lipids in cases of disseminate xanthomatosis might be explained by abnormal storage, the existence of such cases they regarded as opposed to the theory. Furthermore, there are numerous cases in which hyperlipemia has not been associated with cutaneous xanthomas. One of these was reported from the Mayo Clinic by Ochsner and Conner.[6] The patient was a woman 55 years of age. She had been ill for less than two years with cardiac episodes and moderate elevation of the blood pressure. The blood was milky, and examination revealed values for total lipids, total fatty acids and cholesterol of 2,638, 1971 and 667 mg., respectively, per hundred

6. Ochsner, H. C., and Conner, H. M.: Lipemia Accompanied by Atheromatous and Occlusive Vascular Disease: Report of a Case and Partial Review of the Literature, Ann. Int. Med. **10**:258-269 (Aug.) 1936.

cubic centimeters. Six months later an attack of coronary disease proved fatal, the necropsy revealing as the only abnormality an extreme degree of atherosclerosis of the arteries. The liver weighed 1,983 Gm. It was only moderately infiltrated with fat and otherwise was not abnormal. So far as could be determined this patient had always had a well rounded dietary, not unusually rich in fat or cholesterol. The elevation of the lipid content seemed, therefore, to be on the basis of an anomaly of lipid metabolism, and the authors postulated that this was primary and the atherosclerosis secondary. The alternate supposition, that the atheromatous lesions in the arteries were primary and the lipemia was attributable to rupture of atheromatous "abscesses," seems improbable. However, it is possible that atherosclerosis such as this represents xanthomatosis limited to the arteries.

For many years patients with epilepsy have been treated at the Mayo Clinic with the so-called ketogenic diet, in which the content of carbohydrate usually is less than 25 Gm., that of protein not more than 60 Gm. and that of fat, depending on the total number of calories required by the patient, varying up to more than 200 Gm. Such symptoms as those complained of by the patient of Ochsner and Conner have never been encountered in these patients. However, in 2 children who died of other causes, small atheromatous plaques were seen in the arteries. The value for lipids in the blood of patients on the ketogenic diet is almost never abnormally high, but recently my colleagues and I have had experience with a case in which there developed an atypical form of eruptive xanthomatous lesion of the skin associated with hyperlipemia. When the ketogenic diet was discontinued, the abnormality disappeared.

It is my guess from the evidence presented and from other experience that cholesterol production is a function of reticulo-endothelial cells wherever located; that a second function of these cells is to remove cholesterol and other lipids from the blood when the level exceeds what is physiologic, and that in xanthomatosis and possibly also in atherosclerosis some of these cells, because of biologic inferiority, become incapable of disposing of the cholesterol they themselves have made (xanthomatosis without hyperlipemia) or have absorbed from the blood stream (xanthomatosis with hyperlipemia) and thereby take on the appearance of foam cells. The cause of the hyperlipemia may be either an increased rate of synthesis of cholesterol by abnormal reticulo-endothelial cells or a high intake of cholesterol by persons who are incapable of maintaining a normal rate of excretion of cholesterol (Schoenheimer and Hrdina).

Treatment of Cholesterosis.—Little is known about the treatment of conditions associated with excessive accumulation of cholesterol. A

diet restricted in animal fat is sometimes effective, as has previously been stated. Exposure to roentgen rays is said to be of some effectiveness in xanthomatosis of the type not associated with hyperlipemia, and in recent years a number of writers have affirmed that iodine in large doses inhibited the atheromatosis produced in rabbits by feeding them cholesterol. Thiersch,[7] of the pathological institute in Freiburg, has commented on this and has also presented the results of experiments on rabbits with a preparation of a pure extract of garlic, in combination with deoxycholeic acid. Garlic, it seems, is an old "folk remedy" for arteriosclerosis. A dose representing 5 Gm. daily of garlic root was given to 33 animals, together with 0.3 Gm. daily of cholesterol for ninety days. Eleven controls received only the cholesterol. At the end of the trial period the aorta and blood were analyzed for cholesterol. The average values for the rabbits receiving cholesterol and garlic were 185 and 405 mg. per hundred cubic centimeters, respectively. Those for the rabbits receiving only the cholesterol were 543 and 641 mg., respectively.

Xanthomatosis and Hyperlipemia in Diabetes.—In a case reported by Nicholson [8] under the title "Xanthoma Diabeticorum" there were many of the characteristics of the Cushing syndrome. At the age of 21 years the patient gained 80 pounds (36 Kg.) in four months, showed purplish striations of the skin and had weekly headache in both temporal regions. He had held this weight twenty years, and five weeks before examination noticed a papular xanthomatous eruption affecting the entire body except the face. Hypertension, polycythemia, hyperglycemia (207 mg. of sugar per hundred cubic centimeters) and glycosuria were found. There was no acidosis, and the diabetes was so mild that it was controlled without difficulty by a restricted diet and 15 units of insulin. The cholesterol content (total) at the first examination was 543 mg. per hundred cubic centimeters. After four months, the diet having been restricted rigidly as to fat, the cholesterol content (total) had fallen to 262 mg. The ester fraction was high, and no evidence of hepatic disease was obtained. I wonder whether the term xanthoma diabeticorum should be used for cases such as this in which the diabetes is mild. Similar tuberous xanthomas have occurred in patients who had no diabetes, and frequently they have responded to restriction of the intake of fat. Nicholson's patient previously had not been on a diet unusually high in fat, and although glycosuria existed there was no ketosis. It

7. Thiersch, H.: Die Einwirkung des Knoblauchs auf die experimentelle Cholesterin-Atheromatose des Kaninchens, Ztschr. f. d. ges. exper. Med. **99**: 473-477, 1936.

8. Nicholson, W. M.: Xanthoma Diabeticorum, Internat. Clin. **4**:71-77 (Dec.) 1937.

is true that improvement in the xanthomatous eruption followed control of the diabetes, but this control involved restriction of the intake of fat to 40 Gm., which perhaps was more responsible than anything else. Nicholson admitted that the relation in the case of the symptoms of the Cushing syndrome was speculative, and even though Anselmino and Hoffmann claimed, as he said, that extracts of the anterior lobe of the pituitary gland cause hypercholesteremia and ketonemia, their work is not fully substantiated. Hypercholesteremia and ketonemia are not characteristic of the Cushing syndrome, and in Nicholson's case there was no ketonemia. Values for cholesterol (total) of more than 300 mg. per hundred cubic centimeters are rarely obtained for patients with uncomplicated diabetes except when they are in acidosis, and most instances of eruptive xanthomatosis that occur in diabetes are found in patients with acidosis with higher values than this. It seems to me that the term xanthoma diabeticorum might be reserved for them and that cases like that which Nicholson has reported represent an independent disease.

Campbell [9] made the suggestion that a lasting increase in the content of blood fats in diabetes results not when more fat is obtained from the food but when there is an extreme demand for fat as fuel because of the absence of available carbohydrate. Much evidence supports this; however, even in diabetic acidosis values for total cholesterol of more than 300 mg. do not occur with any regularity. In only 22 of Joslin's 94 cases of "coma" did the value exceed that figure.

Xanthomas of the skin are seen infrequently in diabetes, even when the values for the serum lipids are elevated. Nicholson mentioned 1 such instance; a patient at Duke Hospital had a markedly elevated fat content (total cholesterol, 990 mg., per hundred cubic centimeters; cholesterol esters, 513 mg., and total lipids, 8,136 mg.). Marked lipemia apparently will not produce damage to reticular cells unless these originally are inadequate.

Normal Variations in Serum Lipid Values.—Studies from the department of psychiatry of the Yale University School of Medicine by Man, Gildea and their associates [10] indicate that the levels of the lipids of the serum are affected by malnutrition and by fat meals and that they usually are higher for healthy men of pyknic build than for those of the leptosomatic type, but that for the same subject they vary from time to time. In a recent paper report was made of examination at intervals, for periods of three months to four years, of 4 healthy

9. Campbell, J. N. H.: Critical Review: Cholesterol in Health and Disease, Quart. J. Med. **18**:393-422 (July) 1925.

10. Man, Evelyn B., and Gildea, E. F.: Variations in Lipemia of Normal Subjects, J. Biol. Chem. **119**:769-780 (July) 1937.

men and 6 healthy women. The extreme range for the cholesterol values of the serum was from 173 to 236 mg. per hundred cubic centimeters, a difference of 31 per cent. The extreme range for lipid phosphorus values was 23 per cent and for fatty acids 37 per cent. That the differences were not related to hemoconcentration was shown by the fact that the values for the total protein of the blood were not affected in the same manner. No relation was found to the slight changes in weight which occurred in several of the subjects, to the season of the year or, in the case of the women, to the menstrual cycle. The fact is consistent with the usual wide range of normal cholesterol values described by Page, Kirk, Lewis, Thompson and Van Slyke.[11] In cases of malnutrition, on the other hand, when the cholesterol values were found to be below normal for 26 of 31 patients, they varied widely with the state of nutrition in 10 patients who were followed for two to ten weeks; improvement in nutrition was accompanied with an increase of from 32 to 101 mg. per hundred cubic centimeters, even when the first observations were not below the normal range. This and the progressive and consistent variations in the cholesterol values observed by Hurxthal [12] and others after the administration of thyroid to patients with myxedema, after the administration of iodine to patients with hyperthyroidism and after treatment of patients in diabetic acidosis are in sharp contrast to the unaccountable variations of lesser degree shown by the normal subject.

Serum Lipid Values in Diabetes.—In a study of 79 diabetic patients who had no acidosis, Man and Peters [13] found the values of the serum for cholesterol to be normal for 42, below normal for 9 and above normal for 28. There was close correlation with the values for phospholipids, and there was less correlation with the values for fatty acids, but gross changes in one component were reflected in the other. *"The value for cholesterol did not appear to be related to the severity of the diabetes, the fat in the diet or the degree of arteriosclerosis."* The subnormal values appeared for the most part associated with hypoproteinemia in patients who were malnourished. Moderate elevation was observed in obese women, but it appeared to be related to the pattern of obesity rather than to the diet.

Severe hypercholesteremia when encountered in these cases usually was referable to complications. It also occurred in a group of patients

11. Page, I. H.; Kirk, E.; Lewis, W. H., Jr.; Thompson, W. R., and Van Slyke, D. D.: Plasma Lipids of Normal Men at Different Ages, J. Biol. Chem. **111**:613-639 (Nov.) 1935.

12. Hurxthal, L. M., cited by Man and Gildea,[10]

13. Man, Evelyn B., and Peters, J. P.: Lipoids of Serum in Diabetic Acidosis, J. Clin. Investigation **13**:237-261 (March) 1934.

with instability of the vasomotor reactions. Acromegaly existed in 1 case, but in the great majority it was impossible to implicate the pituitary body. In some cases there were symptoms suggesting a lesion of the brain stem (Parkinson syndrome, diabetes insipidus or some other condition). The basal metabolic rate frequently was elevated; nevertheless, most of the stigmas of hyperthyroidism were lacking.[14]

Serum Lipid Values in Diabetic Acidosis.—In diabetic acidosis, dehydration is responsible for many of the abnormalites encountered, including those in the values for the lipids of the blood. Changes in the values for lipids before and after treatment were compared by Man and Peters,[15] with variations in the concentration of serum protein, which were taken as an index of the degree of dehydration. They had demonstrated before that normal capillaries are equally impermeable to proteins and lipids. In 15 cases of diabetes at the height of acidosis the values for cholesterol were above the normal levels for the subjects in question. They fell rapidly during recovery, their fall being paralleled by the course of the values for serum protein in all cases except 3; in these 3 cases the fall was greater than that of the value for protein. The reductions in the values for nonphospholipid fatty acids and lipid phosphorus exceeded those for cholesterol in most cases. The cholesterol value during the height of acidosis was greater than 300 mg. per hundred cubic centimeters in only 5 cases, and when correction was made for hemoconcentration this was true in only 3 cases. Man and Peters, like Campbell, found reason for connecting the increases in the value for fatty acid with carbohydrate starvation, which by increasing the demand for consumption of fat provokes a mobilization of nutritive lipids from depots in the body. This theory they attributed to Blix,[16] who before the introduction of insulin observed that the values for lipids in the serum of diabetic patients were higher before breakfast on the morning after a fast day than they were several hours after the ingestion of bread alone or a breakfast containing 35 to 50 Gm. of fat.

Evidence for a direct effect of insulin on the fatty acids of serum has been sought by a number of investigators with results, according to

14. The question of the relation of cholesteremia to the arteriosclerosis of diabetes, with particular reference to the studies of Duff, Weiss and Minot; Watson and Wharton, and Hunt, who also concluded that the values for blood lipids are not related to the degree of arteriosclerosis in diabetes, was considered in a previous review (Wilder, R. M.: Diseases of Metabolism and Nutrition, Arch. Int. Med. **57**:434-435 [Feb.] 1936).

15. Man, Evelyn B., and Peters, J. P.: Serum Lipoids in Diabetes, J. Clin. Investigation **14**:579-594 (Sept.) 1935.

16. Blix, Gunnar: Studies on Diabetic Lipemia, Acta med. Scandinav. **64**: 142-259, 1926. Page 234 is of particular interest.

Man and Peters, which are unconvincing. Man and Peters reported that for 10 of their patients who did not have acidosis, no difference could be demonstrated between the values for the lipids of the serum before and those obtained one hour after the morning dose of insulin. Thus, what decrease in blood lipid value occurs after treatment of acidosis, beyond that which can be ascribed to hemodilution, is to be attributed, they claimed, to the recognized effect of insulin on carbohydrate metabolism, rather than to any supposititious direct effect on the mobilization or combustion of fat.

Serum Carotene.—Frequently in conditions associated with hyperlipemia, whether xanthomatosis is present or not, the serum and the skin of the patient are yellowed by xanthochrome pigments (carotene and xanthophyll). In a study of the subject made several years ago in the division of medicine of the Mayo Clinic, Boeck and Yater [17] found that in 100 patients with diabetes and 53 patients suffering from other diseases chosen at random, xanthemia occurred in 86 per cent of those with diabetes, in 100 per cent of those with renal disease and in 89 per cent of those with miscellaneous diseases. Xanthosis, on the other hand, defined as yellowing of the skin due to the deposit of lipochrome pigments, was present in 9 per cent of the patients with diabetes (2 of these patients also had xanthomatosis), in 9 per cent of those with renal disease and in 3 per cent of those with other diseases. Of 36 patients whose condition originally was diagnosed as xanthosis, 10 were diabetic, and 26 either had other diseases or, with the exception of the xanthosis, were normal. Thus, these conditions are by no means to be considered manifestations of diabetes, as originally was supposed by von Noorden. Apparently there is a greater tendency for xanthosis to develop when the diabetes is severe, but even severe diabetes may not reveal this complication, and the evidence does not warrant the conclusion that the presence of xanthosis in diabetes unfavorably affects the course of the disease.

What causes xanthosis is unknown. It occurs more commonly when the diet has a high lipochrome content, but individual variation must exist in the ability to oxidize and excrete the pigments, because many patients show neither xanthemia nor xanthoses with diets equally high in lipochromes. There also is insufficient evidence at present to permit attributing the phenomenon to any fault in the metabolism of fat; although xanthosis usually accompanies hyperlipemia and xanthomatosis, it also occurs independently. The ease of oxidation of the pigments themselves is the probable explanation. Palmer [18] showed that

17. Boeck, W. C., and Yater, W. M.: Xanthemia and Xanthosis (Carotinemia): A Clinical Study, J. Lab. & Clin. Med. **14**:1129-1143 (Sept.) 1929.

18. Palmer, L. S.: Carotinoids and Related Pigments: The Chromolipoids, New York, The Chemical Catalog Co., 1922.

oxidation accounts for the normal disappearance of these pigments in both human beings and animals.

Heymann,[19] after determining the content of carotene in the blood serum at intervals after the administration of carotene in oil to 10 diabetic and 12 nondiabetic children, concluded that carotene metabolism is interfered with in diabetes; and Ralli and her co-workers [20] have come to the same conclusion. They explained that the difficulty is due to failure of the liver to convert carotene to vitamin A but offered what seems to me insufficient evidence to establish such a conclusion.

Importance of Fat in Nutrition.—It is important not to be overly alarmed by the evidences of injury from fat foods. It must be remembered, as the Burrs and Miller [21] have emphasized, that the diet of human beings often is exceedingly low in fats of any kind and that many fats in use today contain few acids more unsaturated than oleic acid. It is not improbable that diets high in carbohydrate and protein, by carrying an inadequate amount of unsaturated oils, are contributory factors to the development of dry skin, disturbed renal function, sterility, anemia and other pathologic conditions. The liver apparently is limited in its ability to produce unsaturated fatty acids, and the latter must be obtained through the diet.

OBESITY

Digestion and Absorption of Fat in Obesity.—This subject requires periodic attention because of the popular misconception that obese persons derive more value from the food they eat than do thin persons. Neuenschwander-Lemmer [22] determined the caloric values of the feces and their content of nitrogen and of fat for 3 obese and for 3 control subjects who were of normal weight. The intake of calories purposely was held somewhat below the calculated requirements, and rest in bed was maintained. Under these circumstances the percentage of utiliza-

19. Heymann, Walter: Carotenemia in Diabetes, J. A. M. A. **106**:2050-2052 (June 13) 1936.

20. Ralli, Elaine P.; Branclaleone, H., and Mandelbaum, T.: Studies on Effect of Administration of Carotene and Vitamin A in Patients with Diabetes Mellitus: Effect of Oral Administration of Carotene on Blood Carotene and Cholesterol of Diabetic and Normal Individuals, J. Lab. & Clin. Med. **20**:1266-1275 (Sept.) 1935. Stueck, G. H.; Flaum, Gerald, and Ralli, Elaine P.: The Serum Carotene in Diabetic Patients, with Clinical Evidence of Carotenemia as Determined by the Photo-Electric Colorimeter, J. A. M. A. **109**:343-344 (July 31) 1937.

21. Burr, G. O.; Burr, Mildred M., and Miller, E. S.: On the Fatty Acids Essential in Nutrition, J. Biol. Chem. **97**:1-9 (July) 1932.

22. Neuenschwander-Lemmer, N.: Ueber Ausnutzungsversuche bei fettsüchtigens und normalen Menschen, Ztschr. f. d. ges. exper. Med. **99**:394-398, 1936.

tion by the obese persons averaged 87 for calories, 84 for nitrogen and 83 for fat. The corresponding figures for the controls were 88, 85.5 and 85.5 per cent, respectively. The figures for absorption for both groups were somewhat below those obtained by Atwater. For normal men they were 88.3 to 97.4 per cent for calories, 88.3 to 96.2 per cent for nitrogen and 87.3 to 98.3 per cent for fat.

Ketonuria and Obesity.—Lauter and Neuenschwander-Lemmer,[23] unable to confirm an observation of Kugelman supporting Bergmann's theory of *lipomatoesen Tendenz,* have reported that fat persons respond to feeding with fat oil with a higher than normal concentration of acetone bodies in the blood. On the other hand, support for the conception that in some cases of obesity the stored fat is less available for oxidation has been presented by MacKay and Sherrill,[24] who studied the ketonuria exhibited during fasting by 11 obese and 5 normal subjects. The fasts lasted for four or five days. Four of the obese subjects, whose condition was classified for other reasons as endocrinopathic, excreted appreciably less ketone in grams per square meter of body surface than did normal subjects. For the remainder, whose overweight was classified as simple obesity, the excretion always was great and was usually greater than that for the normal subjects. The authors proposed that the method probably offers a means of classifying obesity on a physiologic basis. "Locked fat," they concluded, is a result of endocrine disturbance, this being suggested by the observation of MacKay and Barnes [25] of the ketogenic activity of certain anterior pituitary extracts and by the demonstration by Best and Campbell [26] that such extracts promote the transportation of fat from the body stores to the liver.

These reports still remain difficult to harmonize with clinical observations. For instance, 2 obese women with a low value for ketone bodies in the urine, reported on by MacKay and Sherrill, "gathered their fat quickly following evidence of ovarian deficiency." If this deficiency represented a phenomenon of the menopause, the anterior lobe of the pituitary gland should have been overactive rather than underactive, and thinness rather than obesity should have been expected. As a matter of fact, whether a woman will become thinner or fatter with the development of ovarian deficiency is unpredictable.

23. Lauter, S., and Neuenschwander-Lemmer, N.: Ueber den Ketonkörpergehalt des Blutes bei Fettsüchtigen und Normalen, Ztschr. f. d. ges. exper. Med. **99:** 745-748, 1936.

24. MacKay, E. M., and Sherrill, J. W.: A Comparison of the Ketosis Developed During Fasting by Obese Patients and Normal Subjects, Endocrinology **21:**677-680 (Sept.) 1937.

25. MacKay, E. M., and Barnes, R. H., cited by MacKay and Sherrill.[24]

26. Best, C. H., and Campbell, J., cited by MacKay and Sherrill.[24]

Another Theory of Obesity.—Even though one grants, as one must, that the caloric balance will determine in the end whether fat is deposited or released from storage in the body as a whole, there still remains to be explained why in some cases fat accumulates selectively in certain regions of the body. It is well known that the fat in lipomas is resistant to withdrawal for utilization even in starvation; also that starvation in cases of lipodystrophy causes a much greater loss of fat from the thin upper half of the body than from the fat legs and buttocks. Hetenyi [27] recently advanced the following evidence in support of Bergmann's theory, according to which the tissues of obese persons possess an increased "lipophilia":

Eighteen patients, 10 of them normal in weight and the others obese, were placed for eight days on a subnutrition diet consisting of 800 Gm. of milk and ten crackers. The lipid level of the blood of the subjects of normal weight was unchanged in general, whereas that of the obese subjects fell 18 to 43 per cent. Also, 30 subjects, 13 of them obese and the others normal in weight, were given in the morning, without other food, 200 Gm. of cream, representing approximately 60 Gm. of fat. For the obese subjects the lipid level of the blood, determined after two, three, four and five hours, increased significantly less than did that for the subjects of normal weight. Also, artificial fever was produced in 12 subjects, 5 of them normal and 7 obese. The content of fat in the blood was increased thereby 15 to 36 per cent for the normal subjects and up to 11 per cent for the obese subjects. Finally, 50 cc. of olive oil was injected subcutaneously into each of 11 subjects, 6 of them obese, and the level of blood lipid was determined at the second, fourth and sixth hours. It increased at one time or another 10 to 48 per cent for the normal subjects and only 1 to 8 per cent for the obese. Among the patients who were given injections of oil were 2 with lipodystrophy. When the oil was injected into an upper extremity in these cases absorption proceeded as in the normal subjects; when it was given into a fatty lower extremity the absorption was similar to that in the obese subjects.

These observations seem to indicate that mobilization of fat from fat depots is resisted in obesity and that deposition is accelerated. The condition seems analogous to the increased stability of deposits of glycogen in the liver and in the muscle in von Gierke's disease (glycogenosis). It seems to me that this conception deserves attentive consideration. The effect after meals of withdrawing from the circulation even a little more fat than usual might well account both for the delayed sense of satiety and for the frequently abnormal taste for

27. Hetenyi, G.: Untersuchungen über die Entstehung der Fettsucht, Deutsches Arch. f. klin. Med. **179**:134-141, 1936.

carbohydrate encountered in obese persons. Energy requirements must be satisfied one way or another, and if part of the food is made less available for metabolism, the result, as is the case in diabetes, inevitably is hunger. A slight tendency in this direction would have a profound effect in the course of time. The theory also will explain the unequal distribution of fat and the undoubted influence on this distribution of the endocrinopathies, thus harmonizing the point of view of those who have insisted on the primacy of the dynamic features of the problem with the point of view of those who stress its endocrinologic and constitutional features.

Heredity in Obesity.—There is a strong disinclination on the part of physicians to accept the thesis, defended most effectively by Newburgh and his associates,[28] that obesity always depends on overeating. So-called endogenous obesity is still regarded by many persons as an entity in which the law of conservation of energy fails to function. What seems mostly to be neglected by those who hold such views is the fact that the water balance in obesity which is associated with endocrine disturbances of various kinds frequently is very unstable. However, heredity must play a part of some kind, and the thing that is inherited, as I [29] have suggested previously, is abnormal irritability in centers of the diencephalon where feelings of hunger and satiety originate. A lesion in this region, such as is produced by encephalitis or a tumor, is followed not uncommonly by a huge gain in weight. Experimental lesions of the diencephalon also have been shown to provoke obesity, so that it seems likely that the degree of irritability of this region may differ within a physiologic range in different normal persons and that the characteristic may be passed from parent to child, much as unusual auditory sensitiveness is known to be transmitted. Supporting this supposition is a report by Gurney [30] of studies on 63 stout women compared with another group of women of approximately the same age periods who had been subjected to about the same physiologic and physical episodes. Pregnancy or a major operative procedure appeared to be the most common factor associated with the onset of obesity in the group of stout women, but approximately the same incidence of these events did not have a like effect in the control group. On the other hand, the incidence of obesity in the parents of the stout women was markedly greater than that in the parents of the controls,

28. Newburgh, L. H., and Johnston, M. W.: Endogenous Obesity: Misconception, Ann. Int. Med. **3**:815-825 (Feb.) 1930; Nature of Obesity, J. Clin. Investigation **8**:197-213 (Feb.) 1930.

29. Wilder, R. M.: Regulation of Weight of the Body, Internat. Clin. **1**: 30-41 (March) 1932.

30. Gurney, R.: The Hereditary Factor in Obesity, Arch. Int. Med. **57**:557-561 (March) 1936.

and a study of the progeny of the two groups showed the following differences: Seventy-three per cent of the 89 offspring from matings of stout persons were stout, whereas only 9 per cent of the 176 offspring of the matings of nonstout persons were stout. Forty-one per cent of the 107 offspring of a stout and a nonstout person were stout.

Joslin has said that he is inclined to attribute the frequency of stoutness in the children of obese parents to habits acquired from eating with the parents rather than to heredity; certainly stout persons appreciate good food more than do nonstout persons, and their children thus are "exposed" to better food. What epicure would hire a thin cook! However, it is probable that something more than habit is involved and that this something, which is acquired by inheritance, gives the stout man a better as well as a more discriminating appetite.

Appetite and Control of Body Weight.—My interest in this subject was aroused again by a paper of MacLagan [31] in which are described experiments with rabbits fed a standard ration of beef pulp, bran and water. The appetite of these animals, for the purpose of description, was defined according to the amount of food eaten in a standard time when an unlimited supply was presented. It normally reached a maximum when the animals had fasted eighteen hours, being less if the fast was longer or shorter than this period. An increase of about 20 per cent was produced by a period of ten days of undernutrition, and an increase of 10 per cent was produced by giving insulin in doses of 10 units. This dose is nearly convulsive in a fed rabbit, and smaller doses were without effect. Maximal depression of the appetite, amounting to 49 per cent, was obtained by giving pitressin in doses of 5 units. Almost as effective depression occurred with a dose of 0.15 Gm. of atropine, namely, 37 per cent. Ephedrine, in a dose of 0.15 Gm., was only slightly depressing, and enterogastrone, an extract of intestinal mucosa, had a temporary effect. Negative results were obtained with pitocin, anterior pituitary extract, "ketodestrin," testicular extract and benzedrine. The conclusion is reached that the effect of these drugs on the appetite is likely to be of no clinical value, except for that of insulin, which already has been widely used for treating thinness. Pitressin and atropine had to be given in rather large doses to produce any effect, the former causing slight diarrhea in 3 of 8 animals and the latter causing full dilatation of the pupils in the doses employed.

Dinitrophenol.—This remedy for obesity apparently has run its course, and the consensus seems to be that the danger attending its use outweighs the advantages. The comprehensive clinical study reported

31. MacLagan, N. F.: The Role of Appetite in the Control of Body Weight, J. Physiol. **90**:385-394 (Sept.) 1937.

by Simkins [32] should be read by any one who contemplates resorting to this drug. The final comment of Simkins was as follows:

In dinitrophenol the medical profession has acquired a remarkable drug, a metabolic agent that is well adapted to both clinical and laboratory research. The problems connected with its unpredictable, and occasionally alarming, reactions in some patients are far from solved. Apparently it is nontoxic to the liver, kidneys and heart in therapeutic dosage. Neutropenias are rare. Peripheral neuritis is rather common but not troublesome. Skin rashes, which are common, no longer excite their quondam fear. Cataracts, whether due to the direct effects of the drug or possibly to some unknown mechanism mediated by it, are common. No loss of weight can be condoned at the price of cataracts, and consequently the indiscriminate clinical use of dinitrophenol should be discontinued at once until the problem of complicating cataracts is solved. The clinical use of dinitrophenol should be reserved for urgent indications only.

Exercise for the Obese Person.—Douthwaite,[33] in one of a series of articles on the management of patients with some of the metabolic diseases, has given the following excellent advice:

Most exercises advised for fat people are almost useless, and in many cases very wasteful of physical effort for the result achieved. Thus, the contortions made familiar to us from our young days by the gymnasium instructor often produce powerful biceps, a deep chest, and strong abdominal recti. They leave out of account entirely the importance of the oblique muscles of the abdomen and the quadratus lumborum. It is the weakening of these muscles, however, which is responsible for the loss of waist line, pendulous belly, and constipation of those possessed of a redundant paunch. Another objection to current bathroom exercises is that they can be practised only in strict privacy, for their employment in the street would inevitably lead to an observation cell.

What, then, are the exercises which we should advise? In the first place, they must involve all the main muscles of the abdominal wall and pelvic floor. Secondly, it should be possible to carry out some of them, at any rate, *during working hours* without attracting undue attention. In my opinion those described by Hornibrook in "The Culture of the Abdomen" are far and away the best. This book is a better prescription for abdominal obesity, and for that matter for constipation, than any drug or combination of drugs. The principle is this: the abdominal muscles can be contracted and relaxed at will without causing gross movements of the trunk. The viscera, however, are thus kept in healthy turbulence, and fat deposits over and in these muscles steadily disappear. The action is much the same as that which produces contraction of the quadriceps femoris without accompanying extension of the knee-joints.

First, the patient should be taught to pull his abdominal wall in and out while standing and while sitting. This activates the recti chiefly, but also to some extent the obliques. Secondly, he should learn to exercise the obliques and quadratus lumborum by standing and drawing the hips and lower ribs together, first on one side then on the other. This is more difficult to learn and at first involves more

32. Simkins, Samuel: Dinitrophenol and Desiccated Thyroid in the Treatment of Obesity: A Comprehensive Clinical and Laboratory Study, J. A. M. A. **108**:2110-2117 (June 19); 2193-2199 (June 26) 1937.

33. Douthwaite, A. H.: The Treatment of Obesity, Brit. M. J. **2**:344-346 (Aug. 15) 1936.

movement, but in time the action can be mastered so that the lateral and posterior abdominal muscles are alternately contracted and relaxed with but little motion of the trunk. Again, they can be carried out eventually in a sitting posture. The patient should be taught to appreciate what is happening by placing his fingertips over the muscles to be exercised. By this means he will grasp the scheme much more quickly and carry it out more efficiently. Thirdly, the pelvic floor should be exercised by alternately drawing up and relaxing the anus. As a sharp contraction of the relevant muscles takes place in both sexes at the end of defaecation and of micturition it can be explained in this way without difficulty. The reason for these exercises is that the pelvic floor is usually weakened in the obese and tends to the production of incontinence of urine in the female, constipation, rectal prolapse and piles.

Lastly, the back must not be forgotten. All fat people eventually develop a bad stance, and a healthy abdominal wall cannot be achieved if its main point of attachment is weak and warped. Insistence should thus be placed on the importance of carrying the head and body erect as a positive means to the desired goal. Now, although many other excellent exercises have been devised, yet only those described above can easily be carried out from time to time during the day. The muscular contractions can be performed while the patient is traveling, while waiting for a bus, sitting at a desk, and even at the dinner table, without exciting comment. The great secret of successful exercises is that they should be capable of being performed at frequent intervals until they become a habit. This is obviously of far greater value than a quarter of an hour's intense boredom of "bedroom jerks."

EXPERIMENTAL DIABETES

Metabolism of Carbohydrate in Depancreatized Dogs.—It is doubtful how much dependence can be placed on metabolic observations made after a severely mutilating operation such as that to be described. Soskin and Levine [34] reported experiments performed on dogs that had fasted for three days and that were then subjected to surgical removal of the intestines and the liver, together with ligation of the ureters. Twelve dogs were depancreatized on the first day of fasting, receiving no insulin. Fifteen dogs were not depancreatized. The evisceration and later experiments were performed with the animals under anesthesia induced by pentobarbital sodium. After two hours had been allowed for recovery from immediate shock, the experiments were started. Dextrose solution was injected at the timed rates necessary to maintain blood sugar at desired levels and samples of blood were taken at half-hour intervals for two to four hours. After the injection the animals were killed, and samples of muscle were secured for determination of the glycogen content. The results showed that when the blood sugar level was high, the depancreatized animals used dextrose as effectively as did the "normal" animals; when the blood sugar level was low, the depancreatized dogs were at a disadvantage. This led

34. Soskin, S., and Levine, R.: A Relationship Between the Blood Sugar Level and the Rate of Sugar Utilization Affecting the Theories of Diabetes, Am. J. Physiol. **120**:761-770 (Dec.) 1937.

Soskin and Levine to the conclusion that the completely depancreatized dog utilizes dextrose as effectively as the "normal" animal and hence supports their assumption that the glycosuria and the other characteristic experimental and clinical phenomena associated with diabetes cannot be ascribed to lack of utilization of sugar by the muscles.

Mirsky and his associates[35] have reported that dextrose injected intravenously into nephrectomized depancreatized dogs not receiving insulin produces ketolytic and nitrogen-sparing effects. The conditions of the experiment were such as to lead to the suggestion that glycogen formation occurred. A similar study has been conducted by Barker and Sweet[36] in such a manner that the respiratory metabolism could be studied as well as the blood. It was found that while pronounced ketone and nitrogen sparing was obtained, the respiratory quotient was not raised and that all the sugar injected could be accounted for by the increased amount of fermentable carbohydrate and lactic acid in the muscle and liver. Some explanation other than oxidation of carbohydrate may be found for the nitrogen-sparing and ketolytic effects observed under the conditions named. As the authors commented:

> It should first be pointed out that decreased protein metabolism is judged in this type of experiment solely on the basis of changes in blood non-protein nitrogen; any unmeasured retention of urea in the liver or in the muscles would give a false picture. Secondly, since protein is ketogenic in pancreatic diabetes, any lowering of protein breakdown might account for some of the ketone sparing. In any case, these changes may be attributed fully as well to the high glucose concentrations produced as to the glycogen deposited.

The experiments indicate that neither the formation of glycogen nor the establishment of a high carbohydrate level of the tissues facilitates the oxidation of sugar by the depancreatized dog.

The commonly accepted criteria for oxidation of ingested carbohydrate are an elevation in respiratory quotient, a corresponding diminution in the amount of extra sugar excreted when dextrose is administered, a protein-sparing action of the sugar and a ketolytic effect. Recent experiments of Barker, Chambers and Dann,[37] conducted on fasting depancreatized dogs, revealed that in the early and intermediate stages there occurred no rise in the respiratory quotient, no nitrogen-sparing effect and no ketolytic action after the administration by mouth of 16

35. Mirsky, I. A.; Heiman, J. D., and Broh-Kahn, R. H.: The Antiketogenic Action of Glucose in the Absence of Insulin, Am. J. Physiol. **118**:290-296 (Feb.) 1937. Mirsky, I. A.; Heiman, J. D., and Swadish, S.: The Nitrogen-Sparing Action of Glucose in Phlorhizin and Pancreatic Diabetes, ibid. **119**:376-377 (June) 1937.

36. Barker, S. B., and Sweet, J. E.: Effects of Carbohydrate Plethora in Experimental Diabetes, Science **86**:270-277 (Sept. 17) 1937.

37. Barker, S. B.; Chambers, W. H., and Dann, Margaret: Metabolism of Carbohydrate in the Depancreatized Dog, J. Biol. Chem. **118**:177-195 (March) 1937.

to 50 Gm. of dextrose in single or divided doses. Also, the extra dextrose recovered in the urine averaged 95 per cent for twenty-one experiments. These results indicated no oxidation of administered sugar. However, in 3 animals in the last stages of inanition, indicated by markedly increased excretion of creatine, typical effects of carbohydrate oxidation were obtained. In 1 of these animals the fasting level for blood sugar was 37 mg. per hundred cubic centimeters and the basal respiratory quotient 81 per cent. In this animal, only three days before the premortal condition, the dextrose test had shown complete lack of oxidation of carbohydrate.

This work, as Barker and his associates indicated, recalls experiments of Hédon [38] in which bread was fed to depancreatized dogs and the fact that high basal quotients were observed by him in the "premortal" stages of fasting. The terminal phases of diabetes in patients who were treated with prolonged fasts in the era before insulin was discovered and who showed hypoglycemia and an elevated respiratory quotient represented the same phenomenon. A famous case in point was that of Cyril K., who was studied intensively at the Russell Sage Institute of Pathology.

Barker and his associates also referred to the fact that Houssay and Biasotti [39] in 3 of 5 depancreatized dogs found the respiratory quotient to be elevated from a basal level of 0.7 to approximately 0.8 after a feeding of 50 Gm. of dextrose. Similar results were obtained by Biasotti for 2 more such animals after intravenous injection of sugar.

A plausible explanation of the paradoxic ability of the moribund organism to oxidize dextrose is provided by these and other recent experimental observations. Extreme cachexia, it is reasonable to suppose, must severely depress not only the activity of the pituitary gland but also the activities of the adrenal cortex and of the thyroid gland. The latter may be involved directly or secondarily as a result of depression of activity of the pituitary gland. It is well known that both the thyroid gland and the adrenal bodies undergo a considerable degree of atrophy when the pituitary gland is destroyed. Under these circumstances the antagonists to what limited primordial capacity the cells may natively possess for oxidizing dextrose are removed, and, in addition, presumably by the same means, the activity of the liver in neodextrogenesis is depressed.

PROTAMINE ZINC INSULIN

Retarded insulin continues to receive much attention in the current journals. I can attempt to review only a few of the many papers now dealing with the subject. The opinion prevails that treatment is improved

38. Hédon, cited by Barker, Chambers and Dann.[37]

39. Houssay, B. A., and Biasotti, A., cited by Barker, Chambers and Dann.[37]

by its use, although occasional patients respond less favorably than others. A comment of Whitehill and Harrop [40] was that patients who are not cooperative and who are lax in the management of their diet do badly with protamine zinc insulin and that such patients will find the use of unmodified insulin safer and on the whole more satisfactory. Also in cases in which diarrhea is a complication and in which absorption of food from the bowel is variable, they said they regard protamine zinc insulin as unsafe. Sherrill and Cope,[41] while admitting that it represents a distinct advance in diabetic treatment, questioned whether any particular advantage is to be gained from it in cases in which formerly an essentially normal balance could be maintained with unmodified insulin. The consensus seems to be that treatment, while improved, has not been simplified. Warvel and Shafer [42] emphasized that the use of protamine zinc insulin requires more effort on the part of the physician.

In cases of more severe diabetes it rarely is possible to obtain satisfactory control with one dose of protamine zinc insulin alone. It thus frequently is necessary also to use some unmodified insulin with it. From experience at the Mayo Clinic and that of Joslin [43] it has been found that the two cannot effectively be combined in the same syringe, and although Lawrence and Archer [44] reported that they had combined them with advantage, I advise against it. Patients find it difficult enough to learn how to measure insulin accurately, and to teach them to draw into one syringe the required amount of one insulin and then to supplement this with a proper amount of a second insulin in most cases is impossible.

Protamine zinc insulin of 80 unit strength recently has been distributed for clinical trial. According to Joslin, and experience at the Mayo Clinic has been the same, it acts just as efficiently as the preparation of 40 units strength heretofore available. Joslin also said that it is less likely to cause induration in the skin. Somewhat more care is necessary to secure a uniform suspension before the dose is withdrawn from the vial; it has a slightly greater tendency to form small clumps.

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40. Whitehill, M. R., and Harrop, G. A.: Experience with Protamine Zinc Insulin, South. M. J. **30**:451-458 (May) 1937.

41. Sherrill, J. W., and Cope, E. F. F.: Observations with Protamine Zinc Insulin and Experimental Studies, Publication of the Scripps Metabolic Clinic, La Jolla, California.

42. Warvel, J. H., and Shafer, M. R.: Protamine Insulin in the Treatment of Diabetes Mellitus, J. Indiana M. A. **30**:325-332 (July) 1937.

43. Joslin, E. P.: Protamine Insulin, J. A. M. A. **109**:497-503 (Aug. 14) 1937.

44. Lawrence, R. D., and Archer, N.: Zinc Protamine Insulin: A Clinical Trial of the New Preparation, Brit. M. J. **1**:487-491 (March 6) 1937.

Magnitude of Doses.—Actually in the experience at the Mayo Clinic there has been less use for 80 unit strength protamine zinc insulin than was anticipated. The diets used as a routine contain only about 150 Gm. of carbohydrate, and with this regimen the large majority of patients require less than 50 units daily. Those that do take more for the most part are unstable, with unpredictable fluctuations in their requirements; for them a safer procedure seems to be to use not more than 50 units of protamine zinc insulin and to depend on one or more injections of supplementary unmodified insulin for the additional requirement. However, other physicians with experience are resorting to much larger doses of protamine zinc insulin. Thus, Duncan [45] said that single doses of 80 to 120 units are not uncommon, and in 1 of several cases of juvenile diabetes reported by Drysdale [46] a balance was obtained with 140 units daily.

Timing the Administration.—The administration of protamine zinc insulin in one dose daily before breakfast, as originally advocated by American and Canadian physicians,[47] has been widely adopted. The principal advantage therein is that a single specimen of urine, that passed before breakfast, then provides a reliable guide to dosage. If it contains sugar, the dose may be stepped up with safety; if it is free from sugar, the possibility of overdosage must be considered, and after a few days with sugar-free morning urine the patient should be given a smaller dose. Treatment with protamine zinc insulin, as Himsworth [48] stated, should have as its first objective the control of the disease during the night and only as a secondary objective the restraint of the exaggerated rises in the sugar content of the body after meals. Lawrence and Archer have expressed the same opinion. Referring to the possibility of securing better results with insulin of still longer action, they suggested that this drug would produce a condition comparable to the rare syndrome of spontaneous hypoglycemia and would provoke a reaction every night. "It is clear," they said, "that the basal dose must be tailing off in strength of action at night."

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45. Duncan, G. G.: Protamine Zinc Insulin and Its Practical Application in the Treatment of Diabetes Mellitus, Bull. Ayer Clin. Lab. Pennsylvania Hosp. **3**:121-137 (June) 1937.

46. Drysdale, H. R.: Protamine Insulin in Juvenile Diabetes, J. A. M. A. **108**:1250-1257 (April 10) 1937.

47. Wilder, R. M.: Clinical Investigations with Insulin Protamine Compound, Proc. Staff Meet., Mayo Clin. **11**:257-258 (April 22) 1936. Campbell, W. R.; Fletcher, A. A., and Kerr, R. B.: Protamine Insulin in the Treatment of Diabetes Mellitus, Tr. A. Am. Physicians **51**:161-173 (May 5) 1936.

48. Himsworth, H. P.: Protamine Insulin and Zinc Protamine Insulin in the Treatment of Diabetes Mellitus, Brit. M. J. **1**:541-546 (March 13) 1937.

On the other hand, Himsworth [49] is said recently to have obtained excellent results by administering protamine zinc insulin at 11 p. m.; the food is then better utilized the next day, and Winnett,[50] for the same reason, has given injections two or three hours before breakfast.

Supplementary Doses of Unmodified Insulin.—Warvel and Shafer found that the single morning injection of protamine zinc insulin was satisfactory for adults taking not more than 30 to 35 units but that supplementary doses of unmodified insulin were required before breakfast and before supper by patients with more severe diabetes. Himsworth agreed. He wrote:

> It is only in mild cases that the new preparations may legitimately be expected to control the disease during the whole twenty-four hours. In cases of severity their action should be reinforced by the administration of ordinary insulin at those times when a sudden influx of sugar from the intestine is found to overwhelm their mild action. An analogy may be drawn between the use of the new insulin and a modern technic in anesthesia. The protamine insulins are comparable to the basal anesthetics whose effect is both mild and prolonged; ordinary insulin is comparable to the volatile anesthetic which is superimposed at times when a stronger control is required.

If one insists on having continuously sugar-free urine when only protamine zinc insulin is being used, chronic hypoglycemia is unavoidable, at least in many cases. The symptoms attending gradual lowering of the blood sugar level may be minimal, so that such hypoglycemia is not always easy to recognize. Conceivably, chronic hypoglycemia also may cause serious damage to the nervous system. I [51] referred in last year's review to Bollman's observations of petechial hemorrhages in dogs that had been made hypoglycemic with protamine zinc insulin. His observation has been confirmed by Sherrill and MacKay.[52] Six dogs which were kept in stuporous condition, with blood sugar values between 20 and 30 mg. per hundred cubic centimeters for twenty-four or forty-eight hours, died even after the value was raised to normal by the giving of sugar. A comment that is of interest and importance has been made by Greenhouse: [53] "Certainly some of our patients feel better when they show some sugar in the urine and feel quite uneasy when

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49. Himsworth, H. P., cited by Joslin.[43]

50. Winnett, E. B.: The Clinical Management of Diabetes Mellitus Using Protamine Zinc Insulin, J. Iowa M. Soc. **27**:150-154 (April) 1937.

51. Wilder, R. M., and Wilbur, D. L.: Diseases of Metabolism and Nutrition: Review of Certain Recent Contributions, Arch. Int. Med. **59**:329-364 (Feb.) 1937.

52. Sherrill, J. W., and MacKay, E. M.: Deleterious Effects of Insulin Shock, Proc. Soc. Exper. Biol. & Med. **36**:515-516 (May) 1937.

53. Greenhouse, B.: Protamine Zinc Insulin, Connecticut M. Soc. **1**:247-252 (May) 1937.

sugar free." If by "some sugar" is meant not more than traces in the tests made later in the day and an occasional trace in the urine before breakfast, I wholeheartedly agree. It seems to me to be important to discriminate between the glycosuria that follows a meal and that which occurs in the night. The former represents the spill from an overfilled vessel; the latter is derived from the stores of glycogen and catabolizing protein. Protamine zinc insulin, as I [54] have shown, prevents the occurrence of periods in the twenty-four hours, especially at night, when the tissues of the diabetic patient treated with insufficiently frequent doses of unmodified insulin are called on to deliver amino-acids for the manufacture of dextrose. Ketosis accompanies the resulting negative nitrogen balance, and it too is avoided. Lawrence and Archer have made a similar comment about protamine insulin:

> A striking feature is complete absence of ketosis throughout the twenty-four hours, much more complete than we have ever obtained by three doses of soluble insulin in severe cases of diabetes. Even during the period of hyperglycaemia and glycosuria after a meal there is no recurrence of ketonuria as judged by the sensitive nitroprusside test. It appears that the worst defect of diabetes, the endogenous production of new sugar and acetone bodies, is incomparably better controlled than ever before.

In view of the nitrogen sparing attributable to the continuous insulin effect that is obtained with protamine zinc insulin and the conceivable danger from chronic hypoglycemia attending overdosage with it, also because, like others, I have seen many patients who were "quite uneasy" when the urine was continuously free from sugar, it seems to me to be unwise when using protamine insulin to insist on a continuously normal value for blood sugar. The procedure for adjusting the doses of insulin which I [55] recommend has been described elsewhere. It probably will be disapproved of by Sindoni,[56] who has said he regards any degree of hyperglycemia as evidence of inability to oxidize dextrose—a debatable question. Because protamine zinc insulin cannot be depended on to prevent the development of high blood sugar levels after meals, Sindoni has not prescribed it alone but only as an adjunct to unmodified insulin. When it is indicated at all it should be given, he has said, on retiring and if necessary also after breakfast, and, whether or not it is used, a dose of unmodified insulin is to be administered fifteen minutes after each meal. Complete control of hyperglycemia, he has maintained, will delay premature arteriosclerosis, will

54. Wilder, R. M.: Clinical Investigations of Insulins with Prolonged Activity, Ann. Int. Med. **11**:13-30 (July) 1937.

55. Wilder, R. M.: A Primer for Diabetic Patients, ed. 6, Philadelphia, W. B. Saunders Company, 1937.

56. Sindoni, A., Jr.: Protamine Insulin Versus Ordinary Insulin, J. A. M. A. **108**:1320-1327 (April 17) 1937.

help to prolong the span of life and will increase resistance to infection. This may be true, but surely such radical control is impossible for the patient who lives at a distance, and if it is attempted away from the hospital it must involve great risk of insulin reactions or chronic hypoglycemia.

Another advocate of perfectly normal levels for blood sugar is Richardson,[57] who has suggested that if a renal threshold is higher than 180 mg. per hundred cubic centimeters, examination of urine should not be depended on to direct the maintenance of a satisfactory adjustment. This, too, may be theoretically advantageous when the patient comes regularly to a clinic; it cannot apply to the isolated rancher, for instance, whose nearest laboratory may be several hundred miles away.

The Diet with Protamine Zinc Insulin.— It has been the experience at the Mayo Clinic that better control usually is obtainable with protamine zinc insulin if not more than 150 Gm. of carbohydrate is included in the diet. Campbell's experience and that of Joslin, referred to in last year's review,[51] as well as that of Ricketts,[58] have agreed with it. However, Rabinowitch,[59] Duncan [45] and others have reported satisfactory results with diets containing as much as 300 Gm. of carbohydrate. It is advantageous under such circumstances, and at times desirable even when less carbohydrate is given, to spread the meals, as Duncan has proposed, by giving the breakfast early, saving a portion of it to be taken in the forenoon and taking a lunch at midday, an afternoon snack, a late supper and food at bedtime. Joslin also has recommended more frequent supplying of food in meals and lunches. Greenhouse [53] has stated that he subtracts from the day's dietary prescription the value of three glasses of milk, one of which is given at 10 a. m., one at 3 p. m. and one at bedtime. Ricketts has subtracted a small amount of carbohydrate from the breakfast for a midmorning feeding, and in two thirds of his cases finds a bedtime meal to be a necessity. Pollack [60] has said that he gives no fruit other than banana at breakfast and some other fruit later in the morning. He has found the carbohydrate of banana to be absorbed more slowly than that of other fruits. Also, he has said that he gives two thirds of the protein of the dietary prescription at the evening meal and extra protein-containing food, such as cheese or meat, at bedtime.

57. Richardson, R., and Bowie, M. A.: Observations on the Effectiveness of Protamine Insulin, Am. J. M. Sc. **192**:764-772 (Dec.) 1936. Richardson, R.: Observations on Protamine Zinc Insulin, ibid. **193**:606-611 (May) 1937.

58. Ricketts, H. T.: Problems Connected with the Use of Protamine Zinc Insulin, Ann. Int. Med. **11**:777-790 (Nov.) 1937.

59. Rabinowitch, cited by Wilder and Wilbur.[51]

60. Pollack, Herbert: Personal communication to the author.

These procedures undoubtedly are useful in "tricky" cases. I object to them for routine management because of the inconvenience they cause the patient. So far as possible one should strive to interfere as little as necessary with customary habits of eating and we in this country are not Europeans.

Protamine Zinc Insulin in Emergencies.—A good many writers hold to the opinion that protamine zinc insulin is disadvantageous in the diabetic emergencies, such as acidosis, infection and operation. Exceptions to this view, as Ricketts has written, are emergencies which arise when patients are already under treatment with protamine zinc insulin. In such cases the basal dose should be continued, and the extra requirement should be met with multiple injections of unmodified insulin. At the Mayo Clinic [54] not only is protamine zinc insulin used in such circumstances, but a moderate dose of it is given in the initial treatment of acidosis and before an operation, even when none has been used before.

Complications Attributable to Protamine Zinc Insulin.—Duncan has cited a personal communication from Dr. F. P. Peck, of Indianapolis, in which he stated that 6 cases of allergy to the protamine component of the new insulin have come to attention. I have not encountered it, although it is my impression that irritation at the site of injection occurs somewhat more frequently with protamine zinc insulin. Usually it does not occur after a few weeks of treatment. When necessary, "special" protamine zinc insulin made from beef can be obtained on application to the manufacturers of insulin. No instance of atrophy of fat has come to my attention, and it is to be hoped that this unsightly deformity will be of less frequent occurrence, owing to the fact that insulin is released from its combination with protamine only after absorption. Vascular accidents from the use of protamine zinc insulin also have not been reported, as far as I can determine.

OTHER INSULINS WITH PROLONGED ACTION

An interesting development was in progress in California at the same time that Hagedorn was experimenting with the protamines. For a number of years, in the division for research on cancer at the Santa Barbara Cottage Hospital, investigation of the relation of hormones to cancer has been carried out under the direction of Ullmann. In the course of this study Bischoff and Maxwell found a certain sample of pituitary gonadotropic extract to be fully ten times more potent than other samples. Eventually this was accounted for by traces of zinc left in the preparation during the process of separation. Eventually it was shown also that absorption of the hormone was retarded by the zinc and that the greater activity depended on this retardation. This

phase of the work was published by Maxwell.[61] The suggestion arose that the same principle might be applied with advantage to insulin; but first, because of apprehension on the score of possible toxicity from such a heavy metal, a search was made for other substances which would have the same effect as zinc. Most of the combinations tried were irritating, but eventually one was found with tannic acid which was fairly satisfactory, as mentioned last year in my review.[51]

This work was in progress when Hagedorn announced his discovery of protamine insulin. Very soon afterward Bischoff[62] found that histone obtained from thymus gland was effective in retarding the action of insulin. The thymus histone precipitated insulin on the alkaline side of the iso-electric point for insulin. The precipitate introduced intravenously produced a blood sugar response approximately the same as that of the original insulin, whereas when given intramuscularly it showed the retarded effect. Diabetes in human beings was well controlled with it, and a "pooling effect" was noticeable after four or five days of daily injections. Histone insulin in these respects behaves much as does protamine insulin. Observations on it in 30 cases of diabetes have been reported by Gray, Bischoff and Sansum.[63] No local or systemic reaction was noted, and an average of two and seven-tenths injections of unmodified insulin was reduced to an average of one and one-fifth injections a day.

II. NUTRITION

By Dr. Wilbur

Advances in nutrition during the past year which may be of particular interest to clinicians have had to do chiefly with chemical and physiologic aspects of the vitamins. It is becoming increasingly clear that such extensive pathologic changes as those which characterize marked states of vitamin deficiency are not common in this country, with the exception of those due to rickets and pellagra. Consequently, there is much interest in the possible frequency, nature and method of recognition of states of moderate and of mild deficiency of vitamins. Such less marked states of deficiency depend principally on physiologic and perhaps slight pathologic changes in the tissues, and attempts are being made to develop satisfactory methods of measuring these

61. Maxwell, L. C.: The Quantitative and Qualitative Ovarian Response to Distributed Dosage with Gonadotropic Extracts, Am. J. Physiol. **110**:458-463 (Dec.) 1934.

62. Bischoff, Fritz: Histone Combinations of the Protein Hormones, Am. J. Physiol. **117**:182-187 (Sept.) 1936.

63. Gray, P. A.; Bischoff, Fritz, and Sansum, W. D.: Treatment of Diabetes Mellitus with Insoluble Insulin Compounds, Ann. Int. Med. **11**:274-284 (Aug.) 1937.

physiologic disturbances in man and in experimental animals. The development of the biophotometric test for vitamin A deficiency and tolerance and saturation tests for vitamin C deficiency seem to be a step in this direction. As yet there is lack of evidence of the actual nutritional significance of slightly abnormal reactions to such tests.

The advances in the past year which were particularly worthy of note were the preparation of vitamin A in crystalline form; the designation of vitamin B_1 as thiamin chloride and of vitamin B_2, or G, as riboflavin by the Council on Pharmacy and Chemistry of the American Medical Association; the demonstration that "endemic" pellagra is the same disease as "secondary" pellagra, that it is due to dietary deficiency and that it responds to the same treatment as does "secondary" pellagra; that pellagra apparently responds promptly to treatment with nicotinic acid, and that vitamin C seems to be closely related to the phenomena of immunity, anaphylaxis and resistance to infection.

VITAMIN A

Vitamin A Requirement of Man.—The daily requirement of vitamin A is still unknown. As stated in the review of last year,[64] it seems unlikely that the requirement of vitamin A or of any of the vitamins will be clearly established for many years. Variability in minimal and optimal requirements and in absorption, storage, utilization and destruction is sufficient under normal physiologic conditions to make it difficult to express in exact figures the requirements of any particular vitamin. However, information obtained within the past year by Jeghers[65] was to the effect that the minimal daily requirement for an adult is 4,000 U. S. P. units of vitamin A. Jeans and his associates[66] noted that 3,000 U. S. P. units of vitamin A daily were sufficient to meet the requirements of 2 boys aged 11 years as judged by photometric tests. These findings are in essential harmony with the recommendation of the Council on Pharmacy and Chemistry of the American Medical Association,[67] which has reiterated its previous stand of approving for advertising purposes cod liver oil which meets the standards given in "New and Nonofficial Remedies, 1936"—the dose of 2 teaspoonfuls daily should contain at least 6,250 and not over 10,000 U. S. P. units of vitamin A.

64. Wilder, R. M., and Wilbur, D. L.: Diseases of Metabolism and Nutrition, Arch. Int. Med. **59**:512-555 (March) 1937.

65. Jeghers, Harold: The Degree and Prevalence of Vitamin A Deficiency in Adults, J. A. M. A. **109**:756-762 (Sept. 4) 1937.

66. Jeans, P. C.; Blanchard, Evelyn, and Zentmire, Zelma: Dark Adaptation and Vitamin A, J. A. M. A. **108**:451-458 (Feb. 6) 1937.

67. The Dosage of Preparations Containing Vitamins A and D, report of the Council on Pharmacy and Chemistry, J. A. M. A. **109**:507 (Aug. 14) 1937.

Attempts to determine the vitamin A requirement of cattle, sheep and swine led Guilbert, Miller and Hughes [68] to the conclusion that the minimum vitamin A requirement to prevent night blindness in these animals is from 6 to 8 micrograms of vitamin A (or 25 to 30 micrograms of carotene) for each kilogram of body weight. Crimm and Short [69] reported that the rate of utilization of vitamin A by the dog is between 157 and 300 U. S. P. units per kilogram of body weight per week.

Chemical Structure and Physiologic Activity.—While the chemical structure and physiologic activity of vitamin A and its close relation to the yellow pigment carotene have been known for some time, the preparation of the vitamin in crystalline form from biologic material or by means of synthesis has been accomplished only in the past year. In January 1937 Holmes and Corbet [70] announced the preparation of a crystalline vitamin A concentrate from fish liver oil, and in October they [71] reported that with the use of purified solvents, low temperatures and special technical procedures they had been able to obtain pale yellow crystals from three different fish oils. Determination of the molecular weight and elementary analysis of these crystals revealed a correspondence with the formula which had already been suggested for vitamin A. Bio-assay of the material indicated that it had a value of 3,000,000 U. S. P. units per gram. Synthesis of vitamin A has been reported by Fuson and Christ [72] and by Kuhn and Morris.[73] The latter workers found that their product was biologically active in daily doses of 0.8 microgram and that it agreed with respect to absorption spectrum and chromatographic behavior with natural vitamin A.

Little information has been added during the past year to the already recognized physiologic relation of vitamin A to epithelial tissues and to the visual purple of the rod cells of the retina. Stern and Salomon,[74] as a result of their studies with ovoverdin, a green pig-

68. Guilbert, H. R.; Miller, R. F., and Hughes, E. H.: The Minimum Vitamin A and Carotene Requirement of Cattle, Sheep and Swine, J. Nutrition **13**:543-564 (May) 1937.

69. Crimm, P. D., and Short, D. M.: Vitamin A Deficiency in the Dog, Am. J. Physiol. **118**:477-482 (March) 1937.

70. Holmes, H. N., and Corbet, Ruth E.: A Crystalline Vitamin A Concentrate, Science **85**:103 (Jan. 22) 1937.

71. Holmes, H. N., and Corbet, Ruth E.: The Isolation of Crystalline Vitamin A, J. Am. Chem. Soc. **59**:2042-2047 (Oct.) 1937.

72. Fuson, R. C., and Christ, R. E.: The Condensation of Beta-Cyclocitral with Dimethylacrolein, Science **84**:294-295 (Sept. 25) 1936.

73. Kuhn, R., and Morris, C. J. O. R.: Synthese von Vitamin A, Ber. d. deutsch. chem. Gesellsch. **70**:853-858, 1937.

74. Stern, K. G., and Salomon, Kurt: Ovoverdin, a Pigment Chemically Related to Visual Purple, Science **86**:310-311 (Oct. 1) 1937.

ment obtained from lobster eggs and apparently chemically related to visual purple, suggested that the rapidity of the regeneration of visual purple under physiologic conditions may be accounted for by the supposition that the primary step in the bleaching process of visual purple is not a denaturation of the protein carrier of the pigment but is perhaps a type of photodissociation like that of the reversible dissociation of ovoverdin. Further studies by Sure and Buchanan [75] of the antagonism of thyroxin and vitamins A and B indicated that vitamin A may not be as potent an antithyrogenic agent as is vitamin B.

Deficiency States.—During the past year there has been much discussion of the incidence, methods of recognition and significance of vitamin A deficiency. It is clearly recognized that states of well developed vitamin A deficiency are uncommon in the United States; consequently, little dependence can be placed on purely clinical observations in the recognition of such deficiency states. Probably the principal reason for this is the fact that, as Jeghers [65] has pointed out, the worst diet which he encountered in clinical practice yielded 900 U. S. P. units of vitamin A daily, and an intake of this amount would probably need to be continued for months or years in order to produce clinically important vitamin A deficiency. In an attempt to produce experimental evidence of vitamin A deficiency in man, Jeghers [65] took large doses of vitamin A and then reduced his intake to 200 U. S. P. units daily. Within six days there was photometric evidence and in five weeks subjective evidence of night blindness. These abnormal findings disappeared within three days during which 100,000 units of vitamin A was consumed daily.

The earliest clinical manifestations of deficiency of vitamin A are related to the eyes and the skin. Jeghers [76] has pointed out that in his experience night blindness, in most instances not previously clearly recognized, has been a factor of considerable importance in causing difficulty in driving an automobile at night. He [65] reported that 12 per cent of a group of 162 medical students showed clinical manifestations of vitamin A deficiency, consisting, in order of frequency, of night blindness, photophobia, dryness of the skin, dryness of the conjunctivae, blepharitis and follicular hyperkeratosis.

Because of the infrequency of clinically recognizable vitamin A deficiency in the United States, efforts have been made by a variety of observers to develop satisfactory clinical or laboratory methods of determining the presence of states of partial or subclinical deficiency

75. Sure, Barnett, and Buchanan, Katharyn S.: Influences of Hyperthyroidism on Vitamin A Reserves of the Albino Rat, J. Nutrition **13**:521-524 (May) 1937.

76. Jeghers, Harold: Night Blindness Due to Vitamin A Deficiency: A Consideration of Its Importance in Traffic Problems, New England J. Med. **216**:51-56 (Jan. 14) 1937.

of this vitamin. In general, such methods may be said to fall into two groups—clinical and pathologic. In the former group, in addition to clinical observations of symptoms of well defined deficiency states, such as those involving the eyes and the skin, may be considered examinations of the adaptation of the eyes to darkness, studies of the vitamin A content of the blood and urine, estimations of the "neutrophilic lag" and therapeutic trials with vitamin A in concentrated or crystalline form. Methods of study of pathologic material which may be helpful in the diagnosis include the histologic examination of tissue post mortem or at biopsy, estimations of the vitamin A content of the liver and other tissues and microscopic studies of cells scraped from the mucous membrane of the conjunctivae, nose and female generative tract or of epithelial cells in the urine.

Since the popularization by Jeans and Zentmire [77] of the biophotometric method of studying the dark adaptation of the eyes as an index of vitamin A deficiency, numerous studies have been reported of the incidence of this deficiency in various groups of the population. While there may be some doubt as to the accuracy with which this method of examination measures the adequacy of the previous intake of vitamin A or is a measure of the degree of vitamin A deficiency, it seems obvious from the number of studies which have been made, from the comparative similarity of the results obtained and from the uniformly beneficial effects of administration of vitamin A concentrate for those who have shown abnormal results of the tests, that the results of such examinations are in some way influenced by the state of metabolism of vitamin A. For a discussion of the physiologic background and the value and technic of the biophotometric method of determining vitamin A deficiency, as well as of other methods of examining the eyes for the purpose of estimating the incidence and degree of this deficiency, one should consult the excellent review of Jeghers [78] or the paper of Maitra and Harris.[79] Jeans and his associates [66] have modified the technic which they originally described and have concluded that the new photometer which they have developed reveals certain defects in the old test, although the principles of the test are sound. While all these tests are subjective and demand a certain amount of intelligence

77. Jeans, P. C., and Zentmire, Zelma: A Clinical Method for Determining Moderate Degrees of Vitamin A Deficiency, J. A. M. A. **102**:892-895 (March 24) 1934.

78. Jeghers, Harold: Night Blindness as a Criterion of Vitamin A Deficiency, Ann. Int. Med. **10**:1304-1334 (March) 1937.

79. Maitra, M. K., and Harris, L. J.: Nutritional Surveys: Vitamin A Deficiency Among School Children in London and Cambridge, Lancet **2**:1009-1014 (Oct. 30) 1937.

and cooperation on the part of the patient, Friderichsen and Edmund [80] have reported further studies of a method evolved by Friderichsen [81] which is entirely objective and which can be utilized in examining infants. It depends on an estimation of the faintest amount of light which will provoke an oculomotor reflex. Further study should be made of this method, because with it subjective responses are eliminated.

In an effort to determine the state of vitamin A nutrition of patients, several investigators have made estimations of the vitamin A content of the blood and urine. These studies are not as yet sufficiently advanced to permit the development of significant conclusions. Methods of analysis which have been used have been principally modifications of the antimony trichloride test. Schneider and Weigand [82] reported that vitamin A is not present in the urine of normal persons even when large doses are administered. However, they found that a large percentage of patients with cancer, tuberculosis and generalized infections eliminate the vitamin as a result of impairment of hepatic function or of a change in renal permeability. Boller, Brunner and Brodaty [83] also found that patients with hepatic and renal disease may eliminate vitamin A in the urine. Indeed, this finding was considered by them as of diagnostic value in these diseases and as always an extremely serious prognostic sign. Somewhat in contrast to these findings are those of Gaehtgens,[84] who observed traces of vitamin A in the urine of 8 of 39 pregnant women. After administration of concentrates of the vitamin to this group of women, larger amounts were eliminated, and the urine of 19 of 30 of these women gave positive results. The excretion of vitamin A did not seem to depend on an increase of the vitamin content of the blood.

The widespread pathologic changes which occur in tissues deprived of an adequate supply of vitamin A are fairly characteristic. Wolbach [85] has recently summarized these changes and has emphasized in

80. Friderichsen, C., and Edmund, C.: Studies of Hypovitaminosis A: II. A New Method for Testing the Resorption of Vitamin A from Medicaments, Am. J. Dis. Child. **53**:89-109 (Jan.) 1937.

81. Friderichsen, C.: Quantitive Investigations of the Resorption of A Vitamin in a Case of *Coeliakie*, Acta pædiat. **18**:377-391, 1936.

82. Schneider, E., and Weigand, E.: Pathological Elimination of Vitamin A in Urine, abstr., J. A. M. A. **108**:1927 (May 29) 1937.

83. Boller, R.; Brunner, O., and Brodaty, E.: Elimination of Vitamin A in the Urine, abstr., J. A. M. A. **109**:1162 (Oct. 2) 1937.

84. Gaehtgens, G.: Ueber die Ausscheidung von Vitamin A in der Gravidität, Klin. Wchnschr. **16**:52-53 (Jan. 9) 1937.

85. Wolbach, S. B.: Vitamin Deficiency Experimentation as a Research Method in Biology, Science **86**:569-576 (Dec. 24) 1937; The Pathologic Changes Resulting from Vitamin A Deficiency, J. A. M. A. **108**:7-13 (Jan. 2) 1937.

particular the profound effect which is to be noted in epithelial tissues. Atrophy and subsequent keratinization of the epithelium are the typical changes observed. The diagnostic value of the presence of keratinized epithelium in scrapings from the conjunctivae and from the vaginal and nasal mucous membranes was mentioned in the review of last year.

Determination of the vitamin A content of the tissues post mortem has been reported to give considerable information in regard to vitamin A deficiency. Moore [86] and Ellison and Moore [87] employed this method of examination in the analysis of the livers of 1,000 adults and of approximately 200 children less than 15 years of age. For adults the average value obtained in the 40 cases of accidental death was 220 U. S. P. units per gram of moist tissue. For infants the average value was only 17 units. Such a wide fluctuation was found for the livers of normal persons that evaluation of the results obtained for the diseased livers was somewhat unsatisfactory. However, those diseases in which the reserves of vitamin A were above normal included thyroid diseases of all types and diabetes in adults and tuberculosis in children. Consistently low concentrations were observed for the livers of adults dying of nephritis, peritonitis, pneumonia, renal and vesical infections and other infectious diseases. The correct interpretation of these findings is not clear, because of the variety of factors which may influence vitamin A metabolism. However, Moore [86] estimated that a human being with a normal vitamin A reserve in the liver could live for six months on a diet completely free from the vitamin and that the amount stored in the liver of the normal person is roughly equal to the amount secreted in breast milk during nine months of lactation.

The incidence of marked vitamin A deficiency in the United States is very small. The supposition that states of partial deficiency may be common is receiving continual emphasis as a result of studies with the biophotometer. For example, in his study of 162 medical students in Boston, Jeghers [65] found that 35 per cent of them had low photometric readings and that 12 per cent actually had clinical manifestations of deficiency. In a group of 149 subjects, including WPA workers, medical students, technicians and graduate nurses, all actively engaged in work and apparently healthy, he [78] found evidence to suggest that 34 per cent were deficient in vitamin A, while in a group of 103 ambulatory hospital patients convalescing from the usual type of diseases, only 33 per cent showed no evidence of deficiency. In Chicago Bar-

86. Moore, T.: The Vitamin A Reserve of the Adult Human Being in Health and Disease, Biochem. J. **31**:155-164 (Jan.) 1937.

87. Ellison, J. B., and Moore, T.: The Vitamin A Reserves of the Human Infant and Child in Health and Disease, Biochem. J. **31**:165-171 (Jan.) 1937.

borka and Wasika,[88] using the biophotometric method of examination for 780 adults, reported that of 80 control subjects, 21 per cent gave evidence of borderline deficiency, while 4 per cent were actually deficient. Among clinic patients, 23 per cent gave evidence of borderline deficiency, and 60 per cent showed actual deficiency. That a close relation exists between the incidence of vitamin A deficiency as determined by the biophotometric test and the economic status of the person tested has been clearcut since the original report of Jeans and Zentmire [77] on the incidence of vitamin deficiency among the school children of Iowa. The studies cited indicate this also, as do those of Maitra and Harris [79] in England. The latter authors reported that among 200 elementary school children in the East of London and in Cambridge, between 22 and 36 per cent were in a category described as "definitely subnormal" in their reaction to the test, whereas in public schools (which correspond to private schools in the United States) none of the boys were definitely subnormal, and only 10 per cent were slightly below normal.

These studies all indicate that states of partial deficiency of vitamin A are more common among persons in the lower economic levels, who for financial reasons and ignorance regarding a proper diet may have an inadequate intake of food. Peculiarities in dietary habits, skipping of meals and poor choice of foods were recognized by Jeghers [65] as factors of great importance predisposing to the development of vitamin A deficiency even among an intelligent group of students.

What is the significance of these observations? Is it actually true that from 30 to 50 per cent or even more of our population receive an intake of vitamin A which is inadequate to meet the optimum physiologic needs? Is it necessary that an individual have a normal response to such a test as the biophotometric test in order to be considered perfectly healthy? These are questions of paramount importance in nutrition, but until much further information is available they cannot be satisfactorily answered.

The treatment of deficiency of vitamin A remains unchanged. Concentrates of the vitamin are available principally in the form of concentrated fish liver oils. Carotene is available as an active therapeutic agent, but larger doses of it than of the vitamin are needed to produce comparable results. A significant principle in the treatment of vitamin deficiency diseases is the use of massive doses of vitamins. Jeghers [65] has confirmed this by observing that the best results were obtained

88. Barborka, C. J., and Wasika, Paul: Vitamin A Deficiency: Results of Dark Adaptation Tests on Seven Hundred and Eighty Adults, read by title before the Central Society for Clinical Research, Chicago, Nov. 5 and 6, 1937.

when 70,000 units daily of vitamin A was taken orally for two weeks, followed by 25,000 units daily until dark adaptation returned to normal.

The relation of vitamin A deficiency to the development of calculi in the urinary tract has been discussed in previous reviews. In the past year studies indicating that such a relation exists have been published by Feldman,[89] but the relation has been denied by Lassen and Olesen [90] and by Oppenheimer and Pollack.[91]

Because the metabolism of carotene has been closely identified with the function of the liver, Clark, Robinson and Schiff [92] attempted to use this substance in testing hepatic function, but they concluded that the results were of no apparent value.

THE VITAMIN B COMPLEX

For the sake of convenience the components of the vitamin B complex will be considered as a group, although the individual constituents differ widely chemically and in their physiologic and therefore in their clinical behavior. Largely as a result of extensive chemical studies, including isolation and synthesis of some of the components, and as a result of biologic research and a clearer understanding of terms, some of the preexisting confusion surrounding the components of the vitamin B complex is becoming clarified. In a recent review of this subject Nelson [93] designated the following components:

1. Vitamin B_1, the antiberiberi vitamin that prevents beriberi in man and polyneuritis in animals.

2. Riboflavin, a compound necessary for growth in chicks and rats and for the prevention of cataracts in rats. It is a component of the oxidation-reduction system of living cells.

3. P-P factor, a nutritional factor effective in the prevention of human pellagra.

4. Filtrate factor, a factor for the prevention of a nutritional dermatosis in chicks. Concentrates which contain this factor have been shown to be effective in the treatment of human pellagra and black tongue in dogs.

5. Vitamin B_3, a factor necessary for rapid gains in weight and normal nutrition of pigeons.

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89. Feldman, J. B.: Dark Adaptation as a Clinical Test, Arch. Ophth. **17**: 648-661 (April) 1937.

90. Lassen, H. K., and Olesen, M.: Significance of A Avitaminosis and Hyperparathyroidism in the Formation of Urinary Calculi, Hospitalstid. **80**:435-443 (April 20) 1937.

91. Oppenheimer, G. D., and Pollack, H.: Attempted Solution of Renal Calculi by Dietetic Measures, J. A. M. A. **108**:349-352 (Jan. 30) 1937.

92. Clark, B. B.; Robinson, J. B., and Schiff, L. J.: Concerning the Use of Carotene as a Liver Function Test, Am. J. Physiol. **119**:288 (June) 1937.

93. Nelson, E. M.: The Components of the Vitamin B Complex, J. A. M. A., to be published.

6. Vitamin B_4, a factor for the prevention of a specific paralysis in rats and chicks.

7. Vitamin B_5, a factor necessary for the maintenance of weight in pigeons.

8. Vitamin B_6, or vitamin H, a factor for the prevention of a nutritional dermatosis in rats.

9. Factor W, a factor necessary for growth of rats.

In another summary of the components of the vitamin B complex Elvehjem [94] listed six factors, namely, vitamin B_1, flavin, the antipellagra factor (B_2, or G), the rat antidermatitis factor (B_6), the antiparalytic factor (B_4) and factor W (the alcohol-ether precipitate factor of Elvehjem, Koehn and Olesen).

Whether or not these "components" represent chemical entities required by certain species of animals and not by others is not clear. Fortunately for clinicians, much of the confusion surrounding this problem will probably vanish with the development of pure crystalline products and a less ambiguous nomenclature. So far only two members of the vitamin B complex, namely, vitamin B_1 and the P-P factor, have been unequivocally linked with deficiency disease in man.

Vitamin B_1 (Thiamin Chloride).—The Council on Pharmacy and Chemistry of the American Medical Association,[95] on the suggestion of R. R. Williams, decided to adopt the name thiamin chloride (bromide, sulfate and so on) as the common name for vitamin B_1, with the proviso that if the International Committee on Nomenclature in 1938 should adopt some other suitable name the Council will feel free to concur in the use of the international name, with thiamin chloride as a synonym. The American Society for Biological Chemists, the American Institute of Nutrition and the Committee on Nomenclature of the American Chemical Society have all tentatively approved the term thiamin, although the term aneurin, introduced by Jansen, of Amsterdam, who first isolated the substance, is widely used on the continent and in England.

Chemistry and Physiology.—The chemical structure of thiamin chloride has been known for several years, and the substance has been synthesized and appears on the market principally in that form. Leong and Harris [96] have evidence that synthetic and natural crystalline vita-

94. Elvehjem, C. A.: Vitamin B Fractions: Their Nomenclature and Functions, J. Nutrition (supp.) **13**:11-12 (June) 1937.

95. Thiamin Chloride, report of the Council on Pharmacy and Chemistry, J. A. M. A. **109**:952 (Sept. 18) 1937.

96. Leong, P. C., and Harris, L. J.: Antineuritic Potency of Synthetic and Natural Crystalline Vitamin B_1 as Determined by the "Bradycardia Method," Biochem. J. **31**:672-680 (April) 1937.

min B_1 are equally potent, as determined by the bradycardia method, and that the antineuritic activity of 2.8 to 3 micrograms of the crystalline substance is equal to that of 1 international unit.

It has long been recognized that the activity of thiamin is closely related to that of the oxidation of carbohydrate and particularly of pyruvic and perhaps lactic acid. In a recent excellent summary of the chemical properties of thiamin, Williams [97] pointed out that not only is it almost certain that the disposal of pyruvic acid by an enzymic decarboxylation is one of the functions of thiamin, but thiamin probably has other broad functions as well, suggesting that it is "one of nature's earlier and more fundamental inventions in the process of evolving life." Further evidence of the oxidative role of thiamin in metabolism is presented by Taylor, Weiss and Wilkins,[98] who found that the elevation of the content of bisulfite binding substances in the blood in certain cases of vitamin B_1 deficiency could not be explained entirely by the presence of acetone, of diacetic acid or of pyruvic acid. McHenry [99] presented a hypothesis suggesting that thiamin is necessary for the synthesis of fat from carbohydrate.

Requirements.—The daily intake of thiamin in food by adults is probably in the neighborhood of 1 to 2 mg. This amount apparently satisfies the requirement of man for the substance, although, as calculated by Cowgill, the need varies with the weight and with the total metabolism of the organism. Cowgill [100] has recently assembled further data on the vitamin B_1 requirements of man. For infants the estimate of the desired intake was based on the amount in mother's milk, which with a maximum thiamin content would be about 80 U. S. P. units daily. The "American Public Yearbook, 1934-1935" recommends a minimum amount of 50 units daily. Cowgill [100] stated that for children the figure for optimum retention of thiamin is six to seven times the minimum which prevents beriberi. He stated that during pregnancy and lactation 10 units for each 100 calories per day is a safe amount to advise. Schlutz and Knott [101] concluded that 20 units of vitamin B_1

97. Williams, R. R.: The Chemistry of Thiamin (Vitamin B_1), J. A. M. A., to be published.

98. Taylor, F. H. L.; Weiss, Soma, and Wilkins, R. W.: The Bisulphite Binding Power of the Blood in Health and in Disease, with Special Reference to Vitamin B_1 Deficiency, J. Clin. Investigation **16**:833-843 (Nov.) 1937.

99. McHenry, E. W.: Vitamin B_1 and the Synthesis of Fat from Carbohydrate, Science **86**:200 (Aug. 27) 1937.

100. Cowgill, G. R.: Vitamin Requirements of Man, J. Nutrition (supp.) **13**:23-24 (June) 1937.

101. Schlutz, F. W., and Knott, E. M.: The Vitamin B Requirement of Children: The Effects of Varied Ingestion of Vitamin B upon the Food Consumption of Children, J. Nutrition (supp.) **13**:13 (June) 1937.

for each kilogram of body weight may be taken tentatively as the optimum requirement for children. In a series of extensive studies Poole, Hamil, Cooley and Macy [102] noted the effect on 193 normal full term infants over the course of one year of doses of thiamin 90 to 100 units (Sherman-Chase) higher than the doses given to an apparently normal control group. They said they felt justified in interpreting the findings as indicating "that increased amounts of vitamin B_1 in the diets of infants did aid in promoting a more stabilized growth and greater nutritional stability." That a wide margin exists between minimal and optimal levels of thiamin requirement is indicated by the work of Knott.[103]

Deficiency States.—Beriberi has been recognized as the classic example of thiamin deficiency in man, and the pathologic changes observed in this disease have been interpreted as evidence of changes characteristic of this deficiency. In summarizing his long experience with this phase of the disease, Vedder [104] pointed out that the three principal changes have to do with the cardiovascular system, the nervous system and anasarca. Death appears to be caused by cardiac hypertrophy followed by sudden dilatation and cardiac failure, and on postmortem examination the right side of the heart is markedly dilated and hypertrophied. Changes in the nervous system are characterized by degeneration of the myelin sheaths of nerve fibers, which is a constant feature and usually affects the majority of fibers. These degenerative changes involve the sympathetic as well as the somatic nervous system.

In the past year there have been numerous papers of interest regarding the clinical features of thiamin deficiency in man. Strauss [105] has summarized the present views on these states of deficiency by indicating that the nervous and circulatory systems are predominantly involved. The diagnoses of alcoholic, diabetic, biliary, gastrogenic and postinfectious polyneuritis, polyneuritis of pregnancy and the Korsakoff syndrome, he concluded, have all concealed the true diagnosis of thiamin deficiency. While symptoms of these conditions may be sudden in onset, they are generally insidious, and the earliest manifestations usually are heaviness of the legs and tenderness of the calf muscles when they are squeezed. Weakness of the limbs, burning of the soles

102. Poole, M. W.; Hamil, B. M.; Cooley, T. B., and Macy, I. G.: Stabilizing Effect of Increased Vitamin B (B_1) Intake on Growth and Nutrition of Infants, Am. J. Dis. Child. **54**:726-749 (Oct.) 1937.

103. Knott, Elizabeth M.: A Quantitative Study of the Utilization and Retention of Vitamin B by Young Children, J. Nutrition **12**:597-611 (Dec.) 1936.

104. Vedder, E. B.: The Pathology of Beriberi, J. A. M. A., to be published.

105. Strauss, M. B.: The Therapeutic Use of Vitamin B_1 in Polyneuritis and Cardiovascular Conditions, J. A. M. A., to be published.

and numbness of the dorsum and lower part of the ankle are next to appear, followed by hypesthesia which advances up the leg and thigh and by atrophy of the muscles and of the skin. Similar changes occur in the upper extremities when they are involved. The differential diagnosis of this form of polyneuritis is usually not difficult, according to Strauss,[105] for in the polyneuritis due to poisoning from heavy metals, particularly lead, the motor nerves and anterior horn cells of the spinal cord are primarily affected. Involvement of sensation is minimal, pain is rare and the upper extremities are more often affected in polyneuritis due to lead poisoning. The first symptoms of thiamin deficiency may appear in alcoholic addicts about twenty days after total absence of thiamin from the diet, according to the observations of Jolliffe, Colbert and Joffe.[106]

The cardiovascular manifestations of thiamin deficiency have been extensively studied by Weiss and Wilkins[107] and consist principally of dyspnea and palpitation on exertion, tachycardia and edema. It is obvious that these manifestations do not, for the present at least, comprise a rigid and easily recognized clinical syndrome, and the diagnosis should not be made without additional evidence in the form of other clinical manifestations of thiamin deficiency, without a history of a grossly inadequate diet, without adequate response to treatment with thiamin or without the determination of certain technical measurements of the circulation. The last-mentioned evidence indicates that, whereas in other forms of congestive failure, except that of hyperthyroidism, there is conspicuous slowing of the circulation, in cases in which there are cardiovascular symptoms due to thiamin deficiency, there is an increase in both the circulation time and the circulatory minute volume.

Other manifestations of thiamin deficiency which have been reported over a period of years include gastro-intestinal changes, such as anorexia, glossitis, achlorhydria and diarrhea, and changes in the blood, such as those indicating anemia. As Strauss[105] has pointed out, there is considerable evidence to suggest that these phenomena are at least in part, if not entirely, manifestations of a deficiency of some portion of the vitamin B complex other than thiamin. In this connection, the

106. Jolliffe, Norman; Colbert, C. N., and Joffe, P. M.: Observations of the Etiological Relationship of Vitamin B (B_1) to Polyneuritis in the Alcohol Addict, Am. J. M. Sc. **191**:515-526 (April) 1936.

107. Weiss, Soma, and Wilkins, R. W.: (*a*) The Nature of the Cardiovascular Disturbances in Vitamin Deficiency States, Tr. A. Am. Physicians **51**:341-373, 1936; (*b*) The Nature of the Cardiovascular Disturbances in Nutritional Deficiency States (Beriberi), Ann. Int. Med. **11**:104-148 (July) 1937; (*c*) Disturbances of the Cardiovascular System in Nutritional Deficiency, J. A. M. A. **109**: 786-793 (Sept. 4) 1937.

studies made by Joffe and Jolliffe [108] on the curves for gastric acidity of 105 chronic alcoholic addicts are of particular interest. These authors stated the opinion that an "achlorhydria preventive factor" may be a part of the vitamin B complex but that this factor is not identical with either thiamin or the pellagra-preventive factor. Sure and Harrelson [109] said they believed that they had conclusively demonstrated in rats that deficiency of the vitamin B complex or of vitamin B_1 associated with varying degrees of paralysis does not lead to any significant change in the rate of peptic digestion, suggesting that, in this species at least, deficiency of the vitamin B complex has no influence on this phase of gastro-intestinal function.

The factor causing the anemia commonly found in association with deficiency of the vitamin B complex has not been clearly established. There is evidence to suggest that it is closely related to the heat-stable portion of the complex known formerly as vitamin B_2 or G and now recognized as consisting of riboflavin, the pellagra-preventive factor and possibly other factors. A report of considerable interest from this standpoint is that of Elsom [110] on the occurrence of macrocytic anemia in a group of pregnant women on a diet adequate in all respects except that in the latter months of pregnancy the intake of vitamin B (whole complex) did not equal that estimated to be adequate according to Cowgill's formula. In the first place, this study indicates clearly that calculations of vitamin B requirement by Cowgill's formula are of definite clinical value, that a characteristic anemia of the macrocytic type will develop in cases of deficiency of this complex and that symptoms involving the nervous and cardiovascular systems and the gastro-intestinal tract occur early in deficiency of the vitamin B complex. The early symptoms noted in these cases were paresthesias or impairment of vibratory sensation; susceptibility to fatigue; edema; tachycardia, and gastro-intestinal symptoms, consisting of anorexia, heartburn or a sense of constant fulness in the epigastrium, alterations of the tongue and constipation. Observations made by Elsom [110] suggested that a diet that is adequate in vitamin B (complex) at the outset of pregnancy may fail to meet the increased demand for that vitamin complex late in pregnancy. Prompt response to the changes in the blood and other organs was obtained by the administration of yeast orally or of liver extract intramuscularly.

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108. Joffe, P. M., and Jolliffe, Norman: The Gastric Acidity in Chronic Alcoholics, Am. J. M. Sc. **193**:501-510 (April) 1937.

109. Sure, Barnett, and Harrelson, R. T.:: Enzymic Efficiency in Avitaminosis: VII. Peptic Digestion in Vitamin B Deficiency, Am. J. Digest. Dis. & Nutrition **4**:177-179 (May) 1937.

110. Elsom, Katherine O'S.: Macrocytic Anemia in Pregnant Women with Vitamin B Deficiency, J. Clin. Investigation **16**:463-474 (May) 1937.

The possibility that thiamin may have some effect on bones, particularly in cases of gout, is voiced by Vorhaus,[111] but confirmation will be needed before such a probability can be accepted as a fact.

The incidence of thiamin deficiency in the United States is unknown. While definitely recognizable beriberi is uncommon, there is some evidence to suggest that states of partial deficiency are not so infrequent. Weiss and Wilkins,[107e] for instance, have reported observation on 120 patients in the Boston City Hospital with beriberi marked by cardiovascular as well as neurologic manifestations. Even more frequently patients are observed with "alcoholic" and other types of polyneuritis which are now recognized as being due to deficiency of thiamin.

Thiamin Therapy.—The prevention of or treatment for states of thiamin deficiency demands the use of foods or of such substances as yeast and wheat germ which are rich sources of thiamin. Crystalline preparations are available for oral or parenteral administration. Daily intramuscular or intravenous injection of 20 to 50 mg. of crystalline thiamin is apparently an adequate therapeutic dose. Larger doses, as much as 90 to 100 mg., have been given without harmful effect. Molitor and Sampson,[112] in their studies of the effects of increased doses of natural and synthetic vitamin B_1 reported that in dogs the minimum dose of vitamin B_1 which is fatal on intravenous administration is 350 mg. per kilogram of body weight. A subcutaneous and oral dose of from six to forty times this amount is needed to produce fatal results, the symptoms of which are shock, muscular tremor, catatonic spasm and disturbed respiration followed by respiratory failure.

In addition to crystalline thiamin, Strauss [105] recommended the use of plain or autolyzed brewers' yeast as a convenient means of administering not only thiamin but other portions of the vitamin B complex. Thirty grams of powdered brewers' yeast of good potency administered three times daily or 6 Gm. of autolyzed brewers' yeast given three times daily is generally adequate in the treatment of patients only moderately ill with deficiency and without apparent abnormalities in gastrointestinal function which would interfere with absorption. In addition, dilute liver extracts, suitable for intramuscular injection, given in doses of 10 to 20 cc. or more daily, are helpful in controlling glossitis and cutaneous manifestations of the type associated with pellagra.

The result of efficient treatment of polyneuritis depends largely on the duration and the extent of the disease. In cases of acute involve-

111. Vorhaus, M. G., cited by Stafford, J.: The Effect of Vitamin B_1 on Bones, Science (supp.) **85**:10 (June 18) 1937.

112. Molitor, H., and Sampson, W. L.: Effects of Increased Doses of Natural and Synthetic Vitamin B_1, Nutrition Abstr. & Rev. **7**:322 (Oct.) 1937.

ment there may be a complete remission of all signs and symptoms in a matter of weeks. However, in cases of advanced polyneuritis the response may be slow, a matter of many months, since it is dependent on regeneration of long nerve fibers. The response of cardiovascular symptoms is often remarkable and almost a matter of hours, although in cases of long-standing involvement, recovery may require several weeks of adequate treatment.

Because of the similarity in certain respects of thiamin deficiency in animals and sickness following roentgen treatment, Martin and Moursund [113] tried the effect of thiamin in these cases, with striking clinical results. Popp [114] has had a similar gratifying experience.

Methods of detecting thiamin deficiencies rest principally on the basis of the previously mentioned clinical changes and on the basis of their disappearance after thiamin therapy. However, certain objective methods of examination may prove useful. Those observers who are interested principally in experimental thiamin deficiency use such methods as the rate of growth in rats, fermentation tests, the bradycardia test and the thiochrome test, which depends on the oxidation of thiamin to thiochrome, which is fluorescent. Meiklejohn [115] has reported a method for estimating the thiamin content of the blood, and there have been several reports of methods of estimating the amount of thiamin in the urine. However, as yet these methods have not been useful as clinical procedures. In the group of cases of vitamin B deficiency reported by Elsom,[110] Lewy [116] noted some interesting chronaximetric changes in the radial nerves, which he found often preceded clinical and hematologic evidence of the deficiency. The degree of change in the peripheral nerves indicated by chronaximetric examination coincided with the severity of the clinical manifestations of deficiency, and improvement in the nerves was noted after vitamin B therapy.

All these methods are indirect and are based on biologic tests which necessarily subject them to some variation. Consequently, it is of great importance that chemical methods of assaying thiamin be developed. Williams [97] stated that it will be no easy matter to devise a satisfactory method of chemical assay for thiamin in foods, for, among other reasons, thiamin occurs in foods in the proportion of from one-

113. Martin, C. L., and Moursund, W. H., Jr.: Treatment of Roentgen Sickness with Synthetic Vitamin B_1 HCl: Preliminary Report, Am. J. Roentgenol. **38**:620-624 (Oct.) 1937.

114. Popp, W. C.: Personal communication to the authors.

115. Meiklejohn, A. P.: The Estimation of Vitamin B_1 in Blood by a Modification of Schopfer's Test, Biochem. J. **31**:1441-1451 (Sept.) 1937.

116. Lewy, F. H.: Chronaximetric Examination in B Avitaminosis During Pregnancy, J. Clin. Investigation **16**:475-477 (May) 1937.

tenth to four parts per million; roughly, it is a thousand times less abundant than vitamin C, and it possesses no known physical property which is adapted to delicate testing. Prebluda and McCollum [117] and more recently Naiman [118] have suggested methods which may prove useful in the chemical assay of this substance.

Riboflavin (Vitamin B_2 or G, Lactoflavin).—The heat-stable portion of the vitamin B complex has been known principally as vitamin G in this country and as vitamin B_2 in England and on the Continent. In recent years it has been demonstrated clearly that this part of the vitamin B complex consists of several factors: a flavin, vitamin B_6 and another substance closely related to, if not in fact, the pellagra-preventive factor of Goldberger. For the flavin factor the term lactoflavin was originally adopted and appears widely in the literature, but in April 1937 the Council on Pharmacy and Chemistry [119] adopted the term riboflavin for this substance to indicate that the compound is a ribose derivative of iso-alloxazine.

Riboflavin is a widely distributed yellow substance with a characteristic green fluorescence; it is found in animal and plant sources of food, particularly in the green leaves of actively growing plants. It is required by the rat for growth and for maintenance of health and probably also by other mammals, including man, although there has been described no specific disease in man due to riboflavin deficiency. Riboflavin has some function in the oxidative processes in cells and, according to Hogan,[120] is probably an essential constituent of the yellow oxidative enzyme that cannot be synthesized by the animal cell.

According to Hogan,[120] the flavin content of organs cannot be increased by administration of large doses of this substance. The body guards its store of riboflavin, although the latter is found in the urine as an excretory product when the diet is normal. Emmerie [121] has estimated that the daily elimination of riboflavin in the urine of man is 819 to 1,250 micrograms. The rate of destruction of riboflavin in the body is unknown, but there is evidence to suggest that some destruction does occur.

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117. Prebluda, H. P., and McCollum, E. V.: A Chemical Reagent for the Detection and Estimation of Vitamin B_1, Science **84**:488 (Nov. 27) 1936.

118. Naiman, Barnet: A Reagent for Vitamin B_1, Science **85**:290 (March 19) 1937.

119. Riboflavin, the Accepted Name for Vitamin B_2, report of the Council on Pharmacy and Chemistry, J. A. M. A. **108**:1340-1341 (April 17) 1937.

120. Hogan, A. G.: Riboflavin: Physiology and Pathology, J. A. M. A., to be published.

121. Emmerie, A., cited by Hogan.[120]

The daily requirement of riboflavin is unknown. Hogan [120] estimated from Emmerie's data that a man should receive from 2 to 3 mg. of riboflavin daily.

The suggestion of Rose [122] is that children up to 10 years of age should receive at least 400 units (Bourquin-Sherman) of riboflavin a day and that adults should receive 200 units daily for each 100 calories consumed. The figures of Rose and of Emmerie and those of Stiebling [123] are essentially in agreement, since Sherman and Lanford [124] estimated that the "Bourquin-Sherman unit" of vitamin G represents about 3 to 5 micrograms of riboflavin. Whether or not larger doses than these will lead to states of better nutrition cannot be judged at present, although, as Sherman [125] has pointed out in rats, the optimal intake of vitamin G (riboflavin) is much higher (probably at least fourfold) than the minimal requirement. Apparently overdoses of riboflavin are not toxic.

There has been much speculation in regard to the possible clinical role of riboflavin. States of deficiency of this substance have not been reported in man. Riboflavin has been reported to be ineffective in the treatment of pellagra in man, and evidently it is neither the intrinsic nor the extrinsic factor in pernicious anemia.

The Pellagra-Preventive Factor; Pellagra.—The etiology of pellagra has been in dispute since the disease was first described. That a dietary factor may be significant has been realized for many years, and, despite important evidence to this effect which has been obtained in the past few years, many clinicians have been of the opinion that endemic pellagra of the South could not be explained solely on the basis of nutritional deficiency. Much confusion has been added to the problem because, as Sebrell [126] has pointed out, there are four postulated factors about which sufficient evidence exists to warrant discussion in connection with the prevention and treatment of pellagra. These are riboflavin; the rat antidermatitis factor, or vitamin B_6; the filtrate factor, or chicken pellagra factor, and the pellagra-preventive (P-P) vitamin, or black tongue-preventive factor.

It has been recognized since the work of Goldberger that the deficiency of a factor called the pellagra-preventive, or P-P, factor could

122. Rose, Mary S.: Laboratory Handbook for Dietetics, ed. 4, New York, The Macmillan Company, 1937.

123. Stiebling, Hazel K., cited by Sherman and Lanford.[124]

124. Sherman, H. C., and Lanford, Caroline S.: Riboflavin: Dietary Sources and Requirements, J. A. M. A., to be published.

125. Sherman, H. C., and Ellis, Lillian N.: Necessary Versus Optimal Intake of Vitamin G, J. Biol. Chem. **104**:91-97 (Jan.) 1934.

126. Sebrell, W. H.: Vitamins in Relation to the Prevention and Treatment of Pellagra, J. A. M. A., to be published.

be related etiologically to at least some cases of pellagra in man. Subsequently it was revealed that the P-P factor and the vitamin B complex are closely related. In the past year there have been two important observations which will probably be of great usefulness in leading to a solution of the problems of the etiology of pellagra and its relation to vitamin B deficiency. These have to do with the observations of Spies, Chinn and McLester,[127] who showed that endemic pellagra, like so-called alcoholic pellagra, responds to the administration of a high caloric and high protein diet, large amounts of yeast and good nursing care, and with the demonstration that nicotinic acid is effective in relieving the symptoms and signs of pellagra.

Spies and his co-workers [127] studied a series of 50 patients with severe endemic pellagra admitted to the hospital for treatment. Forty-seven of the patients recovered when given a high caloric and high protein diet, large amounts of a potent brewers' yeast and general symptomatic and supportive treatment, rest and good nursing care. Each of the 3 patients who died showed at that time healed or healing pellagrous lesions. The specific therapeutic agents used consisted of powdered brewers' yeast in daily quantities of 180 to 270 Gm. (best given in doses of about 20 Gm. each in iced milk) and intravenous injections of liver extract, 20 cc. four or five times daily. The study of these cases seems to indicate clearly that endemic and alcoholic pellagra have the same clinical symptoms and similar lesions and that they respond to the same treatment. They are in fact the same syndrome and constitute a clearly defined deficiency disease. This is an important observation and is of much more than academic interest, for, as Musser [128] has recently stated:

> It is absolutely astounding that statements are made in which it is said that pellagra is rapidly disappearing from the country. Pellagra, according to the United States Public Health Service statistics for 1930, caused more deaths than all the diseases listed as communicable except pneumonia, tuberculosis and influenza.

Perhaps of greater interest and importance are observations of the effect of nicotinic acid in cases of pellagra. Elvehjem and his associates [129] isolated nicotinic acid amide from active concentrates of liver extract and discovered that it, as well as a synthetic preparation of nicotinic acid, was highly effective therapeutically in curing black tongue in dogs. Experiences with it in cases of pellagra in man have been

127. Spies, T. D.; Chinn, A. B., and McLester, J. B.: Severe Endemic Pellagra, J. A. M. A. **108**:853-857 (March 13) 1937; Treatment of Endemic Pellagra, South. M. J. **30**:18-23 (Jan.) 1937.

128. Musser, J. H., cited in The Treatment of Pellagra, editorial, J. A. M. A. **108**:974 (March 20) 1937.

129. Elvehjem, C. A.; Madden, R. J.; Strong, F. M., and Wooley, D. W.: Relation of Nicotinic Acid and Nicotinic Acid Amide to Canine Black Tongue, J. Am. Chem. Soc. **59**:1767 (Sept.) 1937.

highly successful. Spies, Cooper and Blankenhorn [130] have reported the successful use of nicotinic acid by pellagrins in improving and healing the fiery red pellagrous dermatitis, glossitis, stomatitis and vaginitis with nicotinic acid. Since that time Spies [131] has treated 6 additional pellagrins, with excellent results. Smith, Ruffin and Smith [132] have also reported the case of a patient with endemic pellagra who made a dramatic recovery after the administration of nicotinic acid in doses of 60 mg. daily for twelve days. The drug was given intravenously, intramuscularly and orally, and the cost of the total amount administered was only 10 cents.

In some studies reported earlier in the year Ruffin and Smith [133] noted the potency of various liver extracts in the treatment of pellagra. They observed that parenteral administration of liver extract results in subjective improvement of pellagrins but that complete healing of all the phases of the disease will not occur with this method of treatment and that relapse may follow exposure to sunshine. However, a previously ineffective dose of "residue" (what is left of the liver after extraction), in addition to partially effective parenteral treatment with liver extract, results in complete recovery. These findings suggested to Ruffin and Smith that the pellagra-preventive factor is composed of two substances. However, since the studies of nicotinic acid have been reported, it seems reasonable to speculate that nicotinic acid and the pellagra-preventive factor of Goldberger are closely related, if not identical.

The daily requirement of the pellagra-preventive factor is unknown. The pellagra-preventive values of various foodstuffs are tabulated in the paper by Sebrell,[126] including values principally for meat, buttermilk, collards, kale, green peas, tomatoes and tomato juice, turnip greens, wheat germ and yeast.

There is still considerable interest in the relation of sunlight to the cutaneous lesions of pellagra. According to Sebrell,[126] who has recently reviewed the evidence on this subject, sunlight in this disease is to be regarded as an irritant. Smith and Ruffin [134] reported that from statis-

130. Spies, T. D.; Cooper, Clark, and Blankenhorn, M. A.: A Note on the Administration of Nicotinic Acid to Pellagrins, read before the Central Society for Clinical Research, Chicago, Nov. 5, 1937; abstr., J. A. M. A., to be published.

131. Spies, T. D.: Personal communication to the author.

132. Smith, D. T.; Ruffin, J. M., and Smith, Susan G.: Pellagra Successfully Treated with Nicotinic Acid: A Case Report, J. A. M. A. **109**:2054-2055 (Dec. 18) 1937.

133. Ruffin, J. M., and Smith, D. T.: A Clinical Evaluation of the Potency of Various Extracts of Liver in the Treatment of Pellagra, South. M. J. **30**: 4-14 (Jan.) 1937.

134. Smith, D. T., and Ruffin, J. M.: Effect of Sunlight on Clinical Manifestations of Pellagra, Arch. Int. Med. **59**:631-645 (April) 1937.

tical and experimental observations it is concluded that exposure to sunlight of a susceptible subject who has been subsisting on a deficient diet precipitates the acute cutaneous manifestations of pellagra. Beckh, Ellinger and Spies [135] noted that the amount of porphyrins excreted in the urine of alcoholic pellagrins was usually increased above that of normal persons and that the increase bore a rough relation to the intensity of the lesions of the skin and mucous membranes.

The diagnosis of pellagra still rests on clinical ground. While cutaneous lesions and gastro-intestinal and nervous symptoms are usually present in cases of well advanced pellagra and are characteristic of the disease, it is important to remember that all these systems are not necessarily involved in every case, particularly early in the course of the disease. Spies and Cooper [136] have recently presented an excellent summary of the diagnostic features of pellagra and have emphasized the extreme variability of the symptomatology of the early stage of the disease.

Other Components of the Vitamin B Complex.—Nelson [93] has aptly termed this group the "intangible members" of the vitamin B complex. The evidence of the existence of these factors has largely been obtained by such chemical methods as separation effected by selective adsorption and differences in stability to heat in solutions containing varying proportions of acid and alkali, and by such biologic methods as the responses of rats, pigeons and growing chicks fed diets of various types. Whether any of the factors listed earlier in this review are of significance in the nutrition of man is uncertain. Up to the present, deficiency diseases in man resulting from their absence from the diet have not been reported.

VITAMIN C

Of considerable interest to clinicians have been recent studies of the relation of vitamin C to infectious diseases, to immune and anaphylactic phenomena and to hemorrhagic conditions.

Hemorrhage is one of the outstanding clinical features of scurvy, and there has been much discussion of the possible etiologic role of vitamin C subnutrition in a variety of acute and chronic hemorrhagic states. Some clinicians have been inclined to feel that vitamin C subnutrition may be a significant factor in predisposing to hemorrhage, and Rivers and Carlson [137] in their studies of a group of patients with

135. Beckh, W.; Ellinger, P., and Spies, T. D.: Porphyrinuria in Pellagra, Quart J. Med. **6**:305-319 (July) 1937.

136. Spies, T. D., and Cooper, Clark: The Diagnosis of Pellagra, Internat. Clin. **4**:1-11 (Dec.) 1937.

137. Rivers, A. B., and Carlson, L. A.: Vitamin C as a Supplement in the Therapy of Peptic Ulcer: Preliminary Report, Proc. Staff Meet., Mayo Clin. **12**:383-384 (June 16) 1937.

peptic ulcer noted that in cases in which hemorrhage had occurred, the cevitamic acid content of the blood and urine was less than normal. The response to treatment with cevitamic acid was rapid and complete. Rivers and Carlson pointed out that the usual diets given to patients with peptic ulcer are likely to be deficient in vitamin C and that deficiency of the vitamin may play a conspicuous role in the etiology of hemorrhagic gastroduodenal lesions. Similarly, Lazarus,[138] in his studies of 15 cases of peptic ulcer with bleeding, found 13 cases in which evidence of vitamin C subnutrition was present; in 3 cases in which hemorrhage did not occur, the amount of vitamin C excreted in the urine was low also.

In discussing this problem Finkle [139] pointed out that a fairly large proportion of the population suffers from an undersaturation of vitamin C and that there is as yet no evidence to justify the conclusion that vitamin C deficiency has a causal relation to any pathologic condition other than scurvy. Until this problem can be finally settled, perhaps the most reasonable view to take is that while treatment of hemorrhagic conditions with vitamin C should not be carried out with unlimited hope, nevertheless it seems reasonable to advise the use of the vitamin therapeutically in many cases of bleeding. This view is taken because of the ease of administration of the substance and because by so doing at least one possible, even if uncertain, factor which predisposes to or perhaps increases the hemorrhagic tendency can be simply, rapidly and adequately controlled.

Most patients with infections require vitamin C in larger than usual quantities if normal levels are to be maintained in the blood and if normal quantities are to be excreted in the urine. Faulkner and Taylor [140] have indicated that serum levels for cevitamic acid of patients with infections are usually well below those of normal persons. They found that the amount of vitamin C needed to bring the levels of the serum and the urinary output to normal (serum, 0.7 mg. per hundred cubic centimeters; urinary output, 15 to 20 mg. in twenty-four hours) is far greater in the presence of infection than under normal conditions. One patient with active tuberculosis whom they observed required more than 200 mg. of cevitamic acid daily to maintain a normal serum value and a normal urinary output.

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138. Lazarus, Samuel: Vitamin C Nutrition in Cases of Haematemesis and Melaena, Brit. M. J. **2**:1011-1015 (Nov. 20) 1937.

139. Finkle, Philip: Vitamin C Saturation Levels in the Body in Normal Subjects and in Various Pathological Conditions, J. Clin. Investigation **16**:587-593 (July) 1937.

140. Faulkner, J. M., and Taylor, F. H. L.: Vitamin C and Infections, Ann. Int. Med. **10**:1867-1873 (June) 1937.

There has been much speculation as to the role which vitamin C may play in infectious diseases, particularly in regard to the possibility that a state of partial vitamin C deficiency may predispose to the development of an infection and that vitamin C has definite influences on the mechanisms of resistance to infection, including a significant action on the function of the cortex of the adrenal gland. Perla and Marmorston [141] recently reviewed much of the experimental evidence and some of the clinical observations which have been made in this respect and have been able to report certain interesting conclusions. They observed that the influence of vitamin C on resistance to infection is dependent in part on its importance in the production of intercellular cement substance and that because of "the wide distribution of vitamin C in the body, its chemical properties and its influence on tissue respiration, it is suggested that its role in natural resistance to infection is dependent on its physiological importance in the oxidation-reduction process in cellular metabolism." The physiologic and pathologic alterations are expressed clinically by the drop which occurs in natural resistance to spontaneous and induced bacterial infection in the scorbutic state, even though the production of natural or immune antibodies is unaffected (except possibly that of opsonins).

However, in a recently published article, Jusatz [142] reported finding that cevitamic acid under certain conditions is a stimulant to the production of specific antibodies. In rabbits stunted by a diet free from vitamins, he found a reduction in the normal bactericidal titer in the blood serum and a 90 per cent reduction in the power to form specific antibodies. With the administration of vitamins A, B, C and D separately, disappointing results were obtained, since there was no appreciable effect on the ability of the rabbits to produce antibodies. However, when these stunted rabbits were given an intravenous injection of a massive dose of cevitamic acid (33 to 66 mg.), there was a transient rise in the normal (or subnormal) bactericidal index. When the intravenous dose of vitamin C was increased to from 200 to 500 mg., a trebling of bactericidal power could be demonstrated as late as twenty-four hours after the injection, followed by a subsequent fall to the initial titer well before the sixth day. In subsequent studies Jusatz [142] simplified his technic by adding 100 mg. of cevitamic acid to each immunizing dose of horse protein, with the result that an

141. Perla, D., and Marmorston, J.: Rôle of Vitamin C in Resistance, Arch. Path. **23**:543-575 (April); 683-712 (May) 1937.

142. Jusatz, H. J., cited in Cevitamic Acid Stimulation of Specific Antibody Production, editorial, J. A. M. A. **109**:714-715 (Aug. 28) 1937.

average augmentation of fivefold to sevenfold in the production of specific antibodies was noted in the stunted rabbits.

In their discussion of the role of vitamin C subnutrition in tuberculosis and rheumatic infection, conditions in which there has been widespread clinical interest, Perla and Marmorston [141] stated that it has not been unequivocally established "what effect chronic insufficiency of vitamin C in the diet has on natural resistance to a subsequently induced chronic infection such as tuberculosis" and that "it is suggested that undernutrition of vitamin C lowers the natural resistance of man to rheumatic infection and that such a nutritional factor may play a significant etiologic role in this disease." Fundamentally, therefore, the importance of vitamin C in resistance is secondary to its essential role in the maintenance of normal metabolism.

Several papers have been published on studies of vitamin C metabolism in tuberculosis. Abbasy, Harris and Ellman [143] reported a marked lowering of vitamin C excretion in tuberculosis and found that a definite correlation exists between the severity of the tuberculosis judged by usual clinical standards, and the diminution in urinary titers. Martin and Heise [144] made similar observations and concluded that the responsible factors may be an abnormal chemical response of the gastrointestinal tract and an increased requirement of the tissues for vitamin C. These workers received the impression that giving vitamin C improves the prognosis but emphasized that this was only an impression.

Rinehart and his associates [145] have presented further studies of vitamin C in chronic infections, particularly in rheumatic fever and in certain cases of chronic rheumatoid or infectious arthritis. According to their belief, vitamin C deficiency may be a significant factor in the etiology of the two last-mentioned conditions, and the deficiency is the result of a poor intake of vitamin C, anorexia and the digestive disturbances and intoxications of the disease. The studies revealed that the vitamin C values for the blood of patients with rheumatic fever were considerably lower than those for patients with miscellaneous infections. Discussion continues among experts on nutrition and rheumatism as to whether or not the low vitamin C level of the blood of these patients is a matter of cause or effect of the rheumatic disease.

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143. Abbasy, M. A.; Harris, L. J., and Ellman, Philip: Vitamin C and Infection: Excretion of Vitamin C in Pulmonary Tuberculosis and in Rheumatoid Arthritis, Lancet **2**:181-183 (July 24) 1937.

144. Martin, G. J., and Heise, F. H.: Vitamin C Nutrition in Pulmonary Tuberculosis, Am. J. Digest. Dis. & Nutrition **4**:368-374 (Aug.) 1937.

145. Rinehart, J. F.; Greenberg, L. D.; Baker, Frances, and Choy, F.: Vitamin C in Rheumatic Fever and Rheumatoid Arthritis, abstr., J. A. M. A. **109**:1394-1396 (Oct. 23) 1937.

A close relation between vitamin C and other types of infection has been reported in diphtheria by Kumagai,[146] in osteomyelitis by Abbasy, Harris and Hill[147] and in whooping cough by Ormerod, Unkauf and White.[148] Kumagai[146] reported that he was able to reduce the mortality of necrotic diphtheria from 50 per cent to 30 per cent by the intravenous administration of 400 to 600 mg. of vitamin C daily (along with dextrose and epinephrine). Abbasy and his associates found a diminished rate of excretion of vitamin C in the urine of patients with chronic osteomyelitis and a lowered response to a test dose of the substance, indicative of an apparently increased use of the vitamin. Ormerod and his co-workers discovered varying degrees of hypovitaminosis C in whooping cough and said they believed that they were able to decrease markedly the intensity, number and duration of the characteristic symptoms by saturating each patient with vitamin C.

In summarizing their observations on the relation of vitamin C to infections, Abbasy, Harris and Ellman[148] stated that "it is suggested that determination of the vitamin C excretion under controlled conditions may be of use as an index to confirm the presence of an infective state, and also as a prognostic sign to indicate the apparent activity of the disease."

Vitamin C may play a significant role also in anaphylactic reactions, for Lemke[149] demonstrated that the daily administration of vitamin C to guinea-pigs sensitized with horse or sheep serum resulted in the survival of the animals after the reinjection of a dose several times as large as an otherwise fatal dose. Sensitization as well as shock could be inhibited by a single parenteral injection of vitamin C thirty minutes before sensitization or a reinjection was given. The practical application of this observation was demonstrated by Lemke.[150] The serum rash in children with diphtheria who were given 1 cc. of horse serum per kilogram of body weight he was able to reduce considerably by administering 100 to 200 mg. of cevitamic acid by mouth, beginning on the day of the injection.

146. Kumagai, K., cited in Action of Vitamin C in Diphtheria, Foreign Letter, J. A. M. A. **109**:601 (Aug. 21) 1937.

147. Abbasy, M. A.; Harris, L. J., and Hill, N. G.: Vitamin C and Infection: Excretion of Vitamin C in Osteomyelitis, Lancet **2**:177-180 (July 24) 1937.

148. Ormerod, M. J.; Unkauf, B. M., and White, F. D.: A Further Report on the Ascorbic Acid Treatment of Whooping Cough, Canad. M. A. J. **37**:268-272 (Sept.) 1937.

149. Lemke, H.: Modification of Anaphylactic Shock of Guinea Pigs by Vitamin C, abstr., J. A. M. A. **108**:604 (Feb. 13) 1937.

150. Lemke, H.: Beeinflussung des anaphylaktischen Shocks der Meerschweinchen durch C-Vitamin, Nutrition Abstr. & Rev. **7**:346-347 (Oct.) 1937.

Determinations of Vitamin C in the Blood and Urine.—Pijoan and Klemperer [151] have advocated the use of potassium cyanide for preservation of the blood to prevent the loss of cevitamic acid by oxidation when assays are made by titration with 2,6-dichlorophenolindophenol. Blood is collected in tubes containing 5 mg. of potassium cyanide and 10 mg. of potassium oxalate. Speculation that acetylsalicylic acid might influence the urinary content of vitamin C has been denied by Youmans, Corlette, Frank and Corlette.[152] They were unable to demonstrate an increase in the content of vitamin C or of other reducing substances after the injection of 10 to 40 grains (0.65 to 2.6 Gm.) of acetylsalicylic acid.

Because various factors may influence the absorption of vitamin C from the intestine and may therefore interfere with saturation or tolerance tests, Finkle [139] and Wright, Lilienfeld and MacLenathen [153] have advocated the use of intravenously administered test doses. Finkle [139] used a test dose of 100 mg., and in normal persons he observed a rise in the vitamin C output of the urine within two to three hours after the injection to an average of about five times the preinjection level (0.03 to 0.05 mg. per cubic centimeter of urine, or 13 to 20 mg. in twenty-four hours). Finkle [139] concluded that with this technic the measurement of the total urinary excretion of vitamin C for about an eight hour period during the day, including an approximately six hour period after the intravenous injection, suffices to give a true indication of the state of saturation of the body with vitamin C. Wright and his associates [153] used a much larger intravenous test dose—1,000 mg.—and reported that normally 500 mg. or more of the 1,000 mg. test dose is excreted in the urine during the first twenty-four hours and that 400 mg. or more (80 per cent) of this is excreted in the first five hours after the injection. If such a method of intravenous administration of vitamin C proves reliable in determining the state of vitamin C nutrition, it should prove exceedingly useful in the future, because it is relatively simple, it can be carried out in a short time and it is without much source of error.

Clinical Studies.—Intravenously administered test doses of vitamin C have among other advantages that of avoiding influences which may interfere with absorption of vitamin C. That achlorhydria may be such

151. Pijoan, M., and Klemperer, F.: Determination of Blood Ascorbic Acid, J. Clin. Investigation **16**:443-445 (May) 1937.

152. Youmans, J. B.; Corlette, M. D.; Frank, H., and Corlette, M.: Failure of Acetylsalicylic Acid to Effect Excretion of Ascorbic Acid (Vitamin C) in Urine, Proc. Soc. Exper. Biol. & Med. **36**:73-76 (Feb.) 1937.

153. Wright, I. S.; Lilienfeld, Alfred, and MacLenathen, Elizabeth: Determination of Vitamin C Saturation: A Five Hour Test After an Intravenous Test Dose, Arch. Int. Med. **60**:264-271 (Aug.) 1937.

an influence is suggested by the work of Alt, Chinn and Farmer,[154] who measured the cevitamic acid content of the blood of 49 patients with achlorhydria (mostly with pernicious anemia) and found that the mean value was 0.57 ± 0.02 mg. for each hundred cubic centimeters, as compared with a level of 0.79 ± 0.03 mg. for 29 normal or control subjects. Another interesting observation suggesting interference with intestinal absorption of vitamin C was that of Hagmann,[155] who recorded a case of active scurvy in a child 3½ months old who was receiving 4 ounces (120 cc.) of orange juice daily. The symptoms were completely relieved after treatment with vitamin C intravenously, and the child remained well subsequently when orange juice was given by mouth.

A possibly significant role of scurvy in the etiology of chronic subdural hematoma has been raised by Ingalls.[156] In 5 of the 9 cases he observed, roentgenograms of the bones were made, and in 3 cases there were changes characteristic of scurvy of the long bones.

The use of vitamin C as a therapeutic agent in several miscellaneous conditions has been reported recently. Volpe [157] has reported remarkable results following treatment with vitamin C of several patients with intractable psoriasis. Hirata and Suzuki [158] concluded that vitamin C in large doses was definitely helpful in 10 cases of progressive muscular dystrophy.

VITAMIN D

Biochemists have found a fertile field in their studies of sterol derivatives having vitamin D activity. In fact, Bills [159] has recently pointed out that the properties of vitamin D are exhibited by at least ten different sterol derivatives. Two of these are known to be of prime importance in medicine, namely, activated ergosterol and activated 7-dehydrocholesterol. The vitamin D of viosterol, irradiated yeast and yeast milk is identical and consists of activated ergosterol or calciferol. On the other hand, 7-dehydrocholesterol appears to be the principal activatable sterol or provitamin in cholesterol, the chief sterol of animal fats. It therefore comprises the vitamin D present in irradiated milk.

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154. Alt, H. L.; Chinn, Herman, and Farmer, C. J.: The Blood Cevitamic Acid in Patients with Achlorhydria, read before the Central Society for Clinical Research, Chicago, Nov. 5, 1937.

155. Hagmann, E. A.: Active Scurvy in an Infant Receiving Orange Juice, J. Pediat. **11**:480-483 (Oct.) 1937.

156. Ingalls, T. H.: The Role of Scurvy in the Etiology of Chronic Subdural Hematoma, New England J. Med. **215**:1279-1281 (Dec. 31) 1936.

157. Volpe, I.: Ueber mehre Erfolge in der Psoriasis: Behandlung mit Vitamin C, Schweiz. med. Wchnschr. **67**:498-499, 137.

158. Hirata, Y., and Suzuki, K.: Progressive Muscular Dystrophy and Vitamin C, Klin. Wchnschr. **16**:1019 (July 17) 1937.

159. Bills, C. E.: The Chemistry of Vitamin D, J. A. M. A., to be published.

It is produced in the skin on exposure to ultraviolet light, and it is probably the chief, although not the only, form of vitamin D in fish oils. Bills [159] stated that a few of the other forms of vitamin D may have some practical significance, although most of them are of theoretic interest.

Because of the confusion which has existed in regard to the value of various types of milk and other food fortified with vitamin D, the Council on Foods recently reviewed [160] the present status of vitamin D milk. The conclusion which was reached should be helpful to practicing physicians. The Council made the decision that, for the present, milk is the only common food which will be considered for acceptance when fortified with vitamin D. The properties of vitamin D may be imparted to milk by irradiation of the milk, by proper feeding of vitamin D preparations to cows and by direct addition to milk of either natural or manufactured vitamin D concentrates. For those who may be interested in the types of vitamin D milk acceptable to the Council and in the use of vitamin D milk as a food for infants, children and adults, as well as in the requirements and allowable claims for vitamin D milk, reference should be made to this summary by the Council.[160]

Investigators who have studied the problem of rickets and vitamin D deficiency include Hood and Ravitch,[161] who, using irradiated cholesterol in doses of 400 to 775 U. S. P. units of vitamin D, found that as a preventive of rickets it was equal and perhaps superior, unit for unit, to viosterol or cod liver oil. Davidson, Merritt and Chipman [162] found that irradiated evaporated milk was considerably less efficacious for the protection of the premature infant against rickets than was metabolized vitamin D milk when given under identical conditions. This was probably due to the smaller concentration of vitamin D units in the irradiated evaporated milk. Full term infants were practically completely protected from rickets with irradiated evaporated milk.

In their extensive experience with viosterol in the prevention and treatment of rickets, Shelling and Hopper [163] reported, as noted in the previous review,[64] that they did not encounter total refractoriness

160. The Present Status of Vitamin D Milk, report of Council on Foods, J. A. M. A. **108**:206-207 (Jan. 16) 1937.

161. Hood, J. S., and Ravitch, Irene: The Antirachitic Efficacy of Irradiated Cholesterol, J. Pediat. **11**:521-539 (Oct.) 1937.

162. Davidson, L. T.; Merritt, K. K., and Chipman, S. S.: Prophylaxis of Rickets in Infants with Irradiated Evaporated Milk, Am. J. Dis. Child. **53**:1-21 (Jan.) 1937.

163. Shelling, D. H., and Hopper, Katherine B.: Calcium and Phosphorus Studies: XII. Six Years' Clinical Experience with Viosterol in the Prevention and Treatment of Rickets, Tetany and Allied Disorders, Bull. Johns Hopkins Hosp. **58**:137-211 (March) 1936.

to viosterol, and partial refractoriness was noted in 1 case only. Consequently there is considerable interest in the report by Albright, Butler and Bloomberg [164] of a case of rickets resistant to vitamin D therapy. The patient, a boy of 16, had had rickets since the age of 1 year. There was chemical and microscopic evidence of rickets associated with secondary hyperparathyroidism. Failure of the rickets to heal was not due to interference with absorption, since vitamin D given intravenously and by irradiation did not help. However, when massive doses, namely, 150,000 to 1,500,000 U. S. P. units, were given daily by mouth, the disorder was corrected, and healing occurred. Albright and his associates interpreted this case as one due to intrinsic resistance to the antirachitic action of vitamin D.

That disease of the liver may be a factor in the "intrinsic resistance" to the antirachitic effectiveness of vitamin D is suggested by the work of Heymann.[165] After producing hepatic injury in rats by ligating the common bile duct or by intramuscular injections of carbon tetrachloride, he observed that in the former group from ten to twelve times and in the latter group from two to three times as much vitamin D was needed to cure experimental rickets as in a control group. This was not due to alteration in intestinal absorption, because the vitamin was given parenterally; nor was it the result of functional impairment of the osteogenic cells caused by jaundice. The evidence presented by Heymann seems to indicate that normal hepatic function is necessary for the normal metabolism of vitamin D.

It has been presumed for some time that among other functions of vitamin D is that of aiding the absorption of calcium from the intestine. In a recent study of the absorption and excretion of calcium and phosphorus of a patient after ileostomy and colostomy, Johnson [166] reported that no evidence was obtained to indicate that viosterol, in doses of 3 cc. three times a day, had any specific effect on the absorption of calcium from the intestine of an adult.

The rate of individual susceptibility to rickets has not been adequately studied. That in this, as well as in other deficiency diseases, hereditary influences may play a part is suggested by the studies of Streeter, Park and Jackson,[167] who were able by selection and inbreeding to develop

164. Albright, Fuller; Butler, A. M., and Bloomberg, Esther: Rickets Resistant to Vitamin D Therapy, Am. J. Dis. Child. **54**:529-547 (Sept.) 1937.

165. Heymann, Walter: Importance of the Liver for the Anti-Rachitic Efficacy of Vitamin D, Proc. Soc. Exper. Biol. & Med. **36**:812-814 (June) 1937.

166. Johnson, R. M.: The Absorption and Excretion of Calcium and Phosphorus in Three Patients with Colostomy and Ileostomy, J. Clin. Investigation **16**:223-230 (March) 1937.

167. Streeter, G. L.; Park, E. A., and Jackson, Deborah: Hereditary Vulnerability to Dietary Defects in the Development of Bone, Science **85**:437 (May 7) 1937.

two strains of rats that to all appearances were alike save that one of them reacted more severely to a rachitic diet (vitamin D-free, high calcium and low phosphate diet) than did the other strain.

Intoxication with Vitamin D.—Because of the frequent use of massive doses of vitamin D in the treatment of chronic arthritis, hay fever, asthma, pulmonary tuberculosis and other conditions, much interest is attached to the possible toxic effect of such large doses. Steck, Deutsch, Reed and Struck [168] recently reported observations made on 64 dogs and 773 persons who had received massive doses of vitamin D. They concluded that "both human subjects and dogs generally survive the administration of 20,000 units per kilogram per day for indefinite periods without intoxication." They added that hypervitaminosis D first produces cell injury, followed by deposition of calcium, but that the process is reversible and reparable if administration is discontinued promptly. Any suggestion of renal dysfunction is considered by them to be a definite contraindication, as is probably also arteriosclerosis, to the use of excessive doses of vitamin D.

Alleged Decalcifying Effect of Cereals.—One of the most disturbing factors in nutrition of infants has been the apparent decalcifying effect of cereals. Largely because of the work of Mellanby,[169] it has been assumed that cereals contain a substance ("toxamin") which is responsible for the inhibiting effect of cereals on the calcification of bone. While it has been realized that this undesirable effect of cereals can be counteracted with vitamin D, it has seemed advisable to investigate the evidence in regard to the theory of a "toxamin," since cereals make up such a large part of the diet. The Council on Foods [170] has recently reported the results of such an investigation, and the conclusion reached is that there is no good evidence for the existence of a decalcifying factor in cereals and that the hypothesis of the existence of such a factor is not needed to explain experimental results. The concentration of calcium and phosphorus in the diet is just as important as is the ratio of the two substances in determining the occurrence and degree of rickets, and the concentration of phosphorus is determined partly by the amount of available phosphorus in the diet. Cereals contain phosphates in the form of phytin, in which state it is poorly utilized; consequently, if the diet contains a large amount of cereal there is likelihood of an insufficient absorption of phosphate, and rickets is more likely to occur. The Council concluded, therefore, that there "appears

168. Steck, I. E.; Deutsch, H.; Reed, C. I., and Struck, H. C.: Further Studies on Intoxication with Vitamin D, Ann. Int. Med. **10**:951-964 (Jan.) 1937.

169. Mellanby, Edward: Experimental Rickets, Medical Research Council, Special Report Series, no. 61, London, His Majesty's Stationery Office, 1921.

170. The Alleged Decalcifying Effect of Cereals, report of Council on Foods, J. A. M. A. **109**:30-31 (July 3) 1937.

to be no necessity at the present time to irradiate cereals or to add vitamin D substances to cereal products intended for general human consumption in order to overcome the harmful effects of a hypothetical toxin."

Ultraviolet Radiation.—The effects of ultraviolet therapy are widespread, and while much information is lacking in regard to all the specific effects, it is clearly recognized that the value of ultraviolet therapy in rickets is due to the production of vitamin D in the skin. Coblentz [171] and Luce-Clausen [172] have recently reviewed, respectively, the physical and the chemical aspects of ultraviolet therapy. Luce-Clausen has pointed out that ultraviolet radiation is not a strong therapeutic agent in promoting the healing of fractures, nor do exposures sufficient to produce mild erythema and subsequent pigmentation result in beneficial effects in cases of pulmonary tuberculosis.

Toxicity of Cod Liver Oil.—For several years there has been discussion of the possible toxic effect of cod liver oil. Burock and Zimmerman [173] have recently reinvestigated this problem. Using as experimental animals rats and mice, which are supposed to be particularly susceptible to cod liver oil, these workers reached the conclusion that, in view of the small percentage of animals with changes in the tissues, even after the consumption of large doses of cod liver oil, the claim that cod liver oil in therapeutic doses can exert injurious effects cannot be substantiated. Another point of interest which they noted is that Davson [174] has shown that the favorable results observed after the use of cod liver oil in wounds are due not to its vitamin D content but to the action of the oil in stimulating production of granulation tissue.

VITAMIN E

At least three substances possess the effect of vitamin E, and as yet it has not been clearly demonstrated that any one of them is required by man for normal health or reproduction. In fact, the necessity of vitamin E for normal embryonic growth in animals other than the rat and the mouse has not been established. Mattill,[175] in a recent review of the subject, pointed out that vitamin E is associated with antioxidants in nature and that it is readily susceptible to oxidative destruction. More specifically, it seems to play some essential role in

171. Coblentz, W. W.: The Physical Aspects of Ultraviolet Therapy, J. A. M. A., to be published.

172. Luce-Clausen, Ethel M.: Clinical Aspects of Ultraviolet Therapy, J. A. M. A., to be published.

173. Burock, Ethel, and Zimmerman, H. M.: Studies on the Alleged Toxic Action of Cod Liver Oil, J. Nutrition **14**:535-551 (Dec.) 1937.

174. Davson, cited by Burock and Zimmerman.[173]

175. Mattill, H. A.: Vitamin E, J. A. M. A., to be published.

the nuclear activities involving chromatin and is indispensable, especially in tissues in which cellular proliferation and differentiation are unusually rapid.

Of principal clinical interest is the possible etiologic role of a deficiency of vitamin E in threatened and spontaneous abortion and of an excess of the vitamin in malignant disease. Widespread interest has been aroused by the striking report of Rowntree, Lansbury and Steinberg [176] that when rats are fed a crude preparation of ether-extracted wheat germ oil, in addition to an ordinary stock ration, malignant tumors develop which have the character of spindle cell sarcoma and which involve the gastro-intestinal tract and peritoneal cavity. Mattill [175] said that whatever the agent causing these tumors may be, it is not vitamin E.

It is difficult to obtain proof that vitamin E is of value in the treatment of sterility and habitual abortion in human beings. While Shute [177] and others have continued to report satisfactory results with wheat germ oil in the treatment of such conditions as abruptio placentae, it seems reasonable to conclude with Mattill [175] that more clinical evidence is greatly needed to establish the usefulness of vitamin E therapy in abnormal human reproduction.

VITAMIN F

Interest in certain unsaturated fatty acids, such as linoleic acid, at one time known as vitamin F, has been aroused recently because in the advertisements of some cosmetologists it has been suggested that vitamin F is of value in the treatment of many abnormalities of the skin when added to the diet or when applied externally to the skin. Bacharach,[178] who recently reviewed the literature on the subject, found that there is a lack of any well established facts to justify the recommendation of vitamin F to the public for external application to the skin in cosmetics. Somewhat the same stand is taken by the Bureau of Investigation of the American Medical Association,[179] which has reported its investigation of a preparation of this type. However, Weinstein and Glennon [180] stated that these substances may be of value in a number of diseases of the skin, including allergic eczema.

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176. Rowntree, L. G.; Lansbury, John, and Steinberg, A.: Neoplasms in Albino Rats Resulting from the Feeding of Crude Wheat Germ Oil Made by Ether Extraction, Proc. Soc. Exper. Biol. & Med. **36**:424-426 (April) 1937.

177. Shute, Evan: The Early Diagnosis of Abruptio Placentae and Its Treatment with Wheat Germ Oil, Am. J. Obst. & Gynec. **33**:429-436 (March) 1937.

178. Bacharach, A. L.: Vitamin F, Nutrition Abstr. & Rev. **7**:355 (Oct.) 1937.

179. Rats and Vitamin F (?) in Cosmetology, report of Bureau of Investigation, J. A. M. A. **108**:1279 (April 10) 1937.

180. Weinstein, M. L., and Glennon, Katharyn: Vitamin F Ointments, Illinois M. J. **71**:477-479 (June) 1937.

VITAMIN K

Little of clinical significance concerning the usefulness of the antihemorrhagic factor known as vitamin K has been added to that noted in the review last year. Apparently this substance may play some role in the production of prothrombin, for in certain species of animals, deficiency of vitamin K leads to a decrease in the prothrombin content of the blood. The possible importance of this observation in cases of jaundice in which bleeding may be a serious symptom has recently been discussed editorially in *The Journal of the American Medical Association* [181] and is illustrated by the fact that the prothrombin content of the blood of patients with jaundice has been found to be diminished. Since vitamin K is fat soluble and there is frequently interference with the absorption of fat in patients with obstructive jaundice, the possibility has been suggested that the prothrombin deficiency of jaundiced patients may be due to deficiency of vitamin K. So far, studies on this phase of the problem have not been reported, although therapeutic trial is clearly indicated. In fact, with the exception of the report of Dam, Schønheyder and Lewis,[182] who observed no beneficial effect from the use of vitamin K in a case of hemophilia, little is known of the possible influence of the substance in man.

Almquist,[183] who has been actively engaged in studying vitamin K metabolism in chickens, has obtained the antihemorrhagic substance in the form of a colorless crystalline fraction extracted from commercially dehydrated alfalfa. It contains one or two benzene rings. Almquist and Stokstad [184] have also described a rapid procedure for the assay of vitamin K in chicks.

VITAMIN T

A description of possibly another new dietary factor which may be of importance in influencing the blood has been given by Schiff and Hirschberger,[185] who found that it is possible to produce with regularity an increase in the number of platelets in the blood of normal children. The unknown factor responsible for this reaction is present in sesame

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181. Prothrombin Deficiency in Jaundiced Patients, editorial, J. A. M. A. **108**: 2043-2044 (June 12) 1937.

182. Dam, Henrik; Schønheyder, Fritz, and Lewis, Liese: The Requirements for Vitamin K of Some Different Species of Animals, Biochem. J. **31**:22-27 (Jan.) 1937.

183. Almquist, H. J.: Further Studies on the Antihemorrhagic Vitamin, J. Biol. Chem. **120**:635-640 (Sept.) 1937.

184. Almquist, H. J., and Stokstad, E. L. R.: Assay Procedures for Vitamin K (Antihemorrhagic Vitamin), J. Nutrition **14**:235-240 (Sept.) 1937.

185. Schiff, E., and Hirschberger, C.: Thrombocytosis Produced by a Hitherto Unknown Substance—the "Fat-Soluble T Factor," Am. J. Dis. Child. **53**:32-38 (Jan.) 1937.

oil but not in cod liver or olive oil and is therefore not vitamin A. From 8 to 10 drops a day of sesame oil was an effective dose in producing a rise in the platelet count. Schiff and Hirschberger have suggested that this may be a new fat-soluble vitamin, for the present designated as the fat-soluble T factor.

VITAMIN P

Szent-Györgyi,[186] who has played such a prominent part in the isolation and studies of the chemical activity of vitamin C, recently announced that deficiency of vitamin C is not the only factor responsible for experimental scurvy. He stated as his opinion that another substance, which he named vitamin P, although not responsible alone for any clinical symptoms, when present in deficient amounts greatly modifies the pathologic picture of vitamin C deficiency in the experimental animal. Vitamin P appears to be closely related to vitamin C and is a natural companion of vitamin C in plants. Zilva[187] and his associates were unable to confirm these findings.

ANTI-GIZZARD-EROSION FACTOR

In one of his early papers on hemorrhagic disease in chicks, Dam[188] reported among other abnormalities associated with this disease the occurrence of erosion in the gizzard. Recently, because of the great interest in the possible relation of ulcerating lesions of the stomach and duodenum to deficiency syndromes, attention has been focused again on this observation, which has been repeatedly confirmed. It has been shown clearly that the responsible factor is not identical with vitamin K, since the former is thermolabile and is contained in the saponifiable fraction of alfalfa, whereas vitamin K is heat resistant and occurs in the unsaponifiable fraction of alfalfa. The anti-gizzard-erosion factor is found in alfalfa as well as in kale, hempseed, wheat bran and other greens and cereals. Ivy[189] suggested that the primary defect resulting from the deficiency of the anti-gizzard-erosion factor may be resident in the liver rather than in the gastric mucosa. Cheney[190] has reported that the factor is curative as well as preventive of erosion

186. Bentsáth, A.; Rusznyák, S., and Szent-Györgyi, A.: Vitamin P, Nature, London **139**:326-327 (Feb. 20) 1937.

187. Zilva, S. S.: Vitamin P, Biochem. J. **31**:915-919 (June) 1937.

188. Dam, Henrick: Cholesterinstoffwechsel in Hühnereiern und Hühnchen, Biochem. Ztschr. **215**:475-492, 1929.

189. Ivy, A. C.: The Anti-Gizzard-Erosion Factor, Am. J. Digest. Dis. & Nutrition **4**:121 (April) 1937.

190. Cheney, Garnett: Gastro-Enterology in 1936: Selected Topics, Arch. Int. Med. **60**:703-729 (Oct.) 1937.

in the gastric mucosa and that restoration to a normal-appearing mucosa takes place within about three weeks after adequate amounts of alfalfa have been added to the previously deficient diet of chicks with mucosal erosions. As yet there is no evidence to indicate that the anti-gizzard-erosion factor is of importance in man. It seems doubtful that it will prove of much importance in the problem of peptic ulcer, but much clinical observation will be needed to settle this point.

PROTEIN

Interesting work on the biologic aspects and nutritive significance of proteins has been reported by Bergmann and Niemann [191] and by Rose.[192] As a result of extensive studies of amino-acids Rose noted that there are twenty-two common amino-acids; of these, ten are essential, namely, lysine, tryptophan, histidine, phenylalanine, leucine, isoleucine, threonine, methionine, valine and arginine.

The old problem of the protein requirement of man has been reviewed again by Leitch and Duckworth.[193] They have estimated that the requirement for adults on a mixed diet, including animal and plant protein, is about 50 Gm. daily. Evidence is presented which indicates that an intake considerably above this level may be required for the maintenance of health and for a high state of physical development. No evidence has been presented to show that a high protein diet is harmful. Because of these conclusions, which are in fundamental agreement with those of most experts on nutrition, it is of interest to read the report by Strieck [194] of metabolic studies of a healthy man of 70 years who for years had been on a diet containing about 30 Gm. of protein daily. The physical efficiency of this man was excellent, and he maintained a positive nitrogen balance except when sick. In fact, there was no increased excretion of nitrogen after the most strenuous bodily labor. Akyroyd [195] reported that deficiency disease and malnutrition are extremely common in the South of India, and that the children of one group of inhabitants live on tapioca only. The average dietary intake amounts to approximately 2 pounds (900 Gm.) of tapioca a day, which has a

191. Bergmann, Max, and Niemann, Carl: New Biological Aspects of Protein Chemistry, Science **86**:187-190 (Aug. 27) 1937.

192. Rose, W. C.: The Nutritive Significance of the Amino Acids and Certain Related Compounds, Science **86**:298-300 (Oct. 1) 1937.

193. Leitch, I., and Duckworth, J. D.: The Determination of the Protein Requirements of Man, Nutrition Abstr. & Rev. **7**:257-267 (Oct.) 1937.

194. Strieck, F.: Metabolic Studies in a Man Who Lived for Years on a Minimum Protein Diet, Ann. Int. Med. **11**:643-650 (Oct.) 1937.

195. Akyroyd, W. R.: The Assessment of the "State of Nutrition" and the Detection of Malnutrition, Brit. M. J. **2**:1008-1010 (Nov. 20) 1937.

caloric value of 1,500 and contains about 12 Gm. of protein. With this low intake of protein, the children survive, although they are poorly nourished.

IRON

Each year brings a little clearer understanding of the nutritional value of iron and of the relation of deficiencies of iron to anemia. As Heath and Patek [196] have noted in their extensive review of the anemia of iron deficiency, the extent of the deficiency in this disease can be determined quantitatively at any time from the hemoglobin content of the blood, and the deficient factor, iron, can be supplied quantitatively. They have stated that while 12 to 15 mg. of iron daily is usually considered to be an optimal intake, diets containing much less than this amount will maintain the iron balance. Increased demands for iron are noted during growth, pregnancy, lactation and menstruation. The authors expressed the belief that need for iron and loss of iron must play a primary role in the causation of hypochromic anemia, whereas dietary deficiency of iron or malabsorption of iron in a diseased gastrointestinal tract is of secondary importance.

Some other interesting observations and speculations regarding the effectiveness of massive doses of iron in hypochromic anemia have been advanced by Fowler and Barer [197] and by Brock and Hunter.[198] These observers noted that when large amounts of iron were administered, much more iron was absorbed than was converted into hemoglobin. For example, in Fowler and Barer's study an average of 32.6 per cent of the iron administered orally in the form of iron and ammonium citrates was retained, but only approximately 1.96 per cent of the iron administered was utilized in the formation of hemoglobin. In fact, as Brock [199] demonstrated, if smaller than massive doses of iron are administered or if treatment is interrupted prematurely, many patients will not be cured, despite the absorption and deposition of large quantities of the metal.

Following through with this evidence and that produced by their studies of iron metabolism in polycythaemia vera, McCanse and Widdowson [200] have propounded an interesting new theory of the absorption

196. Heath, C. W., and Patek, A. J., Jr.: The Anemias of Iron Deficiency, Medicine **16**:267-350 (Sept.) 1937.

197. Fowler, W. M., and Barer, A. P.: Retention and Utilization of Orally Administered Iron, Arch. Int. Med. **59**:561-571 (April) 1937.

198. Brock, J. F., and Hunter, Donald: The Fate of Large Doses of Iron Administered by Mouth, Quart. J. Med. **6**:5-16 (Jan.) 1937.

199. Brock, J. F.: Relation Between Hypochromic Anemias and Iron Deficiency, Brit. M. J. **1**:314-320 (Feb. 13) 1937.

200. McCanse, R. A., and Widdowson, E. M.: The Fate of the Elements Removed from the Blood-Stream During the Treatment of Polycythemia by Acetyl-Phenyl-Hydrazine, Quart J. Med. **6**:277-286 (July) 1937; Absorption and Excretion of Iron, Lancet **2**:680-684 (Sept. 18) 1937.

and excretion of iron. They have concluded that the body has little power of excreting iron and that the metabolism of iron under normal circumstances is governed by the control of iron absorption rather than by the excretion of iron. The concentration of iron in the plasma is normally low, and when it rises, the excess is stored. The concentration of iron in the intestine of a person on a normal diet is usually so low that the diffusion gradient is not steep enough for much absorption to occur unless the concentration in the body fluids and tissues is subnormal, as in anemia following hemorrhage. When iron is administered in massive doses the diffusion gradient in the intestine rises, and a positive balance is established. It is believed that the bone marrow is sluggish in hypochromic anemia and that it is stimulated only by the presence of a high concentration of iron, which it is difficult for the plasma to maintain because of the storage capacities of certain organs. The threshold phenomenon is consequently one of a threshold of marrow stimulation rather than of intestinal absorption. Barer and Fowler [201] have indicated that patients with achlorhydria show a decreased retention of iron with an ordinary dietary intake of iron but that achlorhydria does not influence the retention of iron when large amounts are given by mouth. The addition of hydrochloric acid did not increase the retention of iron with either a high or a normal intake of iron.

Another interesting problem in iron metabolism which seems a little closer to solution concerns the mechanism which prevents more than the expected degree of anemia in infants after birth and during the period when milk is the principal if not the only source of nourishment and the intake of iron is not equal to the demands. Previously it has been suspected that the store of iron in the liver serves as the reservoir to "carry over" the blood during this period, but recently it [202] has been observed that the hepatic reserve is not so large as was previously thought to be the case and that the demand for iron is satisfied by conservation of that which is present in erythrocytes destroyed during the early months of life.

COBALT

That cobalt may be one of the "little things" in nutrition is suggested by the observations of Denham [203] that domestic animals in New Zealand which have "bush sickness" may be treated with amazing suc-

201. Barer, A. P., and Fowler, W. M.: Influence of Gastric Acidity and Degree of Anemia on Iron Retention, Arch. Int. Med. **59**:785-792 (May) 1937.

202. Iron Metabolism in Early Infancy, editorial, J. A. M. A. **109**:279 (July 24) 1937.

203. Denham, H. G.: Cobalt Investigation in New Zealand, Science **85**:383 (April 16) 1937.

cess by the addition of traces of cobalt to the diet. Kato [204] said that cobalt when administered in doses of approximately one tenth that of iron appeared to accelerate the formation of erythrocytes and hemoglobin in the blood of infants with nutritional anemia.

ZINC

Hove, Elvehjem and Hart [205] studied zinc deficiency in rats and were able to prevent it by giving 40 micrograms of zinc daily. They postulated that zinc is involved in the production or utilization of some hormone of the pituitary gland which controls the motility and tonus of the intestinal tract.

POTASSIUM AND MAGNESIUM

Since Addison's disease is being successfully treated by several measures, one of the most useful of which is a diet low in potassium, it is of interest to note the report of Schrader, Prickett and Salmon [206] on the effects of potassium and magnesium deficiency in the rat. Characteristic symptomatic and pathologic changes developed in these animals and resulted in death in an average of three to five weeks. The deficiency of potassium and magnesium in these animals was marked, while in patients with Addison's disease the intake of potassium is usually reduced to 2 Gm. daily. Wilder [207] has reported that at the Mayo Clinic no untoward effects have been observed in patients with Addison's disease treated with a low potassium diet.

CALCIUM

There have been two reports of interest during the past year in regard to the calcium requirements of man and the value of calcium therapy in dentistry.

Leitch,[208] of the Imperial Bureau of Animal Nutrition of the Rowett Research Institute, in Aberdeen, has summarized the available evidence on the calcium requirements of man. He found that the maintenance requirement of calcium for adults is estimated as 0.55 Gm. daily (Sherman estimated it as 0.45 Gm.). There is no evidence to show

204. Kato, K.: Iron-Cobalt Treatment of Physiologic and Nutritional Anemia in Infants, J. Pediat. **11**:385-396 (Sept.) 1937.

205. Hove, E.; Elvehjem, C. A., and Hart, E. B.: The Physiology of Zinc in the Nutrition of the Rat, Am. J. Physiol. **119**:768-775 (Aug.) 1937.

206. Schrader, G. A.; Prickett, C. O., and Salmon, W. D.: Symptomatology and Pathology of Potassium and Magnesium Deficiencies in Rats, J. Nutrition **14**:85-104 (July) 1937.

207. Wilder, R. M.: Personal communication to the author.

208. Leitch, I.: The Determination of Calcium Requirements of Man, Nutrition Abstr. & Rev. **6**:553-578 (Jan.) 1937.

what additional allowance is required "for health," but it is probable that such an allowance should be made. Leitch said the evidence suggests that senile osteoporosis may be due in part, at least, to calcium deficiency and that the daily minimum gross requirements, assuming a maximal probable retention of 50 per cent of the intake, is as follows:

Age	Gm.
6 months to 2 years	0.8
2 to 9 years	0.9
9 to 15 years	1.0
15 to 16 years	2.0
16 to adult age	Gradual decrease to adult level

In another summary of the present situation in regard to calcium therapy in dentistry the Council on Dental Therapeutics of the American Dental Association [209] made the following report:

1. All the calcium and phosphorus requirement for average needs, including pregnancy and growth, may be suitably obtained by means of an adequate diet containing not only calcium and phosphorus but also other necessary factors, such as caloric, protein and other mineral and vitamin requirements. 2. There is no carefully controlled evidence that the addition of calcium and phosphorus compounds, whether inorganic or organic, promotes retention of these elements and hence freedom from dental disorders except in known cases of deficiency. 3. There is no evidence that the injection of combinations of calcium and phosphorus in addition to diets adequate in these elements promotes the development of sound teeth in the human fetus. The calcification of teeth is a postnatal event.

THE SIGNIFICANCE OF MILD FORMS OF DEFICIENCY DISEASES

Modern clinicians, public health experts, hygienists, experts in dietetics and others interested in public health may well feel confused about the real significance of much of the information that is so rapidly accumulating in the field of nutrition. How is one to meet the major problems of nutrition which Minot said "concern supplying a diet optimal in multiple factors for each given individual at each stage of life"? We are also reminded that "nutrition intimately concerns the welfare of man and his place in future history will depend in no small part on what he decides to eat." One almost wonders how man was successful in keeping alive and healthy during the thousands of years preceding the past twenty-five years, which have seen the dawn of the "newer knowledge of nutrition." Perhaps one explanation may be the wide limits which exist in the capacity of the animal organism to meet its environment. However, an interesting editorial entitled "Brown

209. Council on Dental Therapeutics of the American Dental Association, cited in Calcium Therapy in Dentistry, editorial, J. A. M. A. **108**:1655-1656 (May 8) 1937.

Bread Versus White," which has been published in a recent number of the *British Medical Journal*,[210] offers another explanation. By means of careful estimations of the vitamin B_1 content of brown bread and of white bread and of the rations of bread consumed by soldiers and by citizens of Great Britain many years ago as compared with those consumed today, it was found that the change in character and consumption of bread alone has caused a reduction in available vitamin B_1 from 550 to less than 60 international units a day (500 international units probably represents the physiologic requirement). It was estimated that the ration of the soldier in 1670 contained 1,000 international units of vitamin B_1 a day and that in 1782 the diet of the parish poor contained 660 to 850 units. Indeed, the best-fed members of the population today, while receiving twice as much vitamin B_1 as is received by persons with a low income, consume less vitamin B_1 than did the parish poor of the eighteenth and early nineteenth centuries.

Publication of several reports of nutritional surveys of various groups of the population of this country and of England suggests that malnutrition and deficiency diseases are common. On the other hand, it is difficult to convince skeptics who are not of this belief, because criteria are still indefinite and a standard of the state of nutrition is dfficult to define. Some progress is being made in this direction, however. During the World War and in the postwar period, such simple physical characteristics as weight, height and age were taken to indicate the nutritional status of the individual. As knowledge of the vitamins advanced, previous criteria of nutritional standards have been modified to include the presence or absence of gross evidence of deficiency disease; and as information has accumulated leading to interest in the physiologic changes which occur before gross pathologic changes become manifest in deficiency disease, the problem of the assessment of nutrition has become increasingly more difficult.

Reports of methods of assessing the nutritional status of individuals have been published by McCollum [211] and by the Health Organization of the League of Nations.[212] Methods of assessing the incidence of certain phases of deficiency disease have been reported by many workers, as noted previously in this review. Some of these indicate that apparently minor physiologic alterations, such as slight impairment of the ability to adapt the eyes to darkness or a content of vitamin C in

210. Brown Bread Versus White, editorial, Brit. M. J. **2**:752-753 (Oct. 16) 1937.

211. McCollum, E. V.: Nutrition and Public Health, Proc. Ann. Conf., Milbank Memorial Fund, April 1937, pp. 61-75.

212. Report on the Work of the Group of Experts Appointed to Study Methods of Assessing the State of Nutrition in Infants and Adolescents, Bull. Health Organ., League of Nations **6**:129-204 (April) 1937.

the blood and urine below so-called normal levels, are common even among such well fed persons as Americans. Those who present these physiologic changes are usually unaware of them, and special tests are required for their detection. These changes can usually be corrected by administration of the vitamin which is deficient, but, again, the subject may notice no effect after such treatment.

What is the significance of these findings? Does it matter if otherwise normal persons have such slight physiologic alterations? As the *Lancet* stated editorially,[213] "the physiologist will be quite sure that it does." The answer is that no one knows, but that such changes are probably significant seems reasonable to believe, for, as Minot [214] has well expressed it:

> If the optimal, not usual, diet for man at all ages and under varying circumstances of his activity and environment were known, and if throughout generations each person took an ideal diet—one nicely adjusted with respect to all its constituents at an optimal level for the best possible achievement—not only would much illness be prevented but the physical and mental development of man would be improved, leading to consequences of vast importance.

Latent Deficiency Disease.—In previous sections of this review it was pointed out that it has been possible by selection and inbreeding to develop two strains of rats that in appearance were alike save that one of them reacted more severely to a rachitic diet than the other. This is a rather startling example of the effects of inbreeding and selection and illustrates the fact that some of the characteristics which make up individual variations are the result of fundamental and inheritable reactions of living things. In this connection, recent studies reported by Bloomfield [215] and by French and Bloomfield [216] are of considerable interest. Bloomfield observed that when a series of rats of the same breed and of approximately the same age were placed on a defective diet, there was great individual variation in the loss of weight. Since on repetition of the experiment after the loss of weight had been restored by a normal diet, the rats which lost the most weight in the first instance tended to do so again, it is suggested that resistance to loss of weight with a defective diet seems to be in some cases a characteristic of the individual and not a matter of chance. From observations of a somewhat similar character, French and Bloomfield reported that rats which had lost weight as a result of a defective diet

213. An Objective Test of Nutrition? editorial, Lancet **2**:1025 (Oct. 30) 1937.

214. Minot, G. R.: Harvard and Nutrition, New England J. Med. **215**:1147-1149 (Dec. 17) 1936.

215. Bloomfield, A. L.: Individual Variations in Susceptibility to Dietary Deficiency, J. Nutrition **14**:111-116 (Aug.) 1937.

216. French, L. R., and Bloomfield, A. L.: "Latent Deficiency" in Rats: Variations in Weight Loss on Repeated Feeding of a Defective Diet, J. Nutrition **14**: 117-129 (Aug.) 1937.

and had then been restored to "normal" by stock rations showed a more rapid loss of weight if placed on the same deficient diet for a second time. It is remarkable to note that this unexplained phenomenon of "secondary rapid weight loss" will occur after as long an interval as eighty days between the first and the second period of defective dietary intake. These findings present experimental evidence in keeping with clinical observations that the undesirable influence of a faulty diet in the zone of partial deficiency may become detectable only after years or generations and that a deficient diet may impair considerably the vigor and resistance of the individual for some period after resumption of a normal diet.

Sprue.—In the review published last year, note was made of the remarkable effect of liver extract on the appearance of the gastric mucosa of patients with pernicious anemia and on the motor functional activity of the small intestine of patients with sprue without anemia. Barker and Rhoads [217] have extended the latter studies to include the effect of liver extract on the absorption of fat in sprue. They stated that they were inclined to feel that in sprue, liver extract exerts some specific effect on the absorptive power of the intestinal tract, because in 3 of 5 cases of sprue, previous inability to absorb fat in normal quantities was overcome, and the postabsorptive levels of fat in the blood approached the normal.

MISCELLANEOUS OBSERVATIONS

Reports of the Council on Foods of the American Medical Association.—During the past year the Council on Foods of the American Medical Association has issued a series of reports which summarize in a judicial way information of considerable interest in regard to certain phases of nutrition. These include reports entitled "The Nutritional Significance of the Curd Tension of Milk," [218] "The Nutritional Value of Spinach," [219] "The Alleged Decalcifying Effect of Cereals" [170] and "Strained Fruits and Vegetables in the Feeding of Infants." [220] In summarizing the evidence on the significance of the curd tension of milk, the Council made the following statement:

> In general, milk that has a low curd tension as determined by appropriate laboratory methods leaves the stomach more quickly than milk that does not

217. Barker, W. H., and Rhoads, C. P.: The Effect of Liver Extract on the Absorption of Fat in Sprue, Am. J. M. Sc. **194**:804-810 (Dec.) 1937.

218. The Nutritional Significance of the Curd Tension of Milk, report of the Council on Foods, J. A. M. A. **108**: 2040-2041 (June 12); 2122-2123 (June 19) 1937.

219. The Nutritional Value of Spinach, report of Council on Foods, J. A. M. A. **109**:1907-1909 (Dec. 4) 1937.

220. Strained Fruits and Vegetables in the Feeding of Infants, report of Council on Foods, J. A. M. A. **108**:1259-1261 (April 10) 1937.

have this property . . . The evidence is meager, however, that any soft curd milks are "better digested" or more completely digested than ordinary boiled milk.

The gist of the report on the alleged decalcifying effect of cereals has been noted in the section on vitamin D. In summarizing the evidence on spinach the Council noted that:

Spinach may be regarded as a rich source of vitamin A and as a contributor of vitamin C, iron and roughage to the diet . . . While the total iron content of spinach is high as compared with other vegetable foods, the evidence shows that this iron is not wholly available and is not well utilized by infants. Evidence regarding the amount of the iron of spinach that is available to older children and adults has not been reported at the present time. The calcium of spinach is not well utilized by the organisms because it is present largely in the form of calcium oxalate, which is insoluble in the fluids of the alimentary tract.

Summaries or Symposia of Importance in Nutrition.—During the past year there has appeared a book entitled "The Avitaminosis" by Eddy and Dalldorf [221] which covers most of the chemical, clinical and pathologic aspects of the vitamin deficiency diseases. For those who may be interested in some of the recent advances in nutritional research, particularly with regard to the chemistry of vitamins, reference may be made to an article by McCollum.[222] Another excellent summary of nutrition and of deficiency diseases is that published by a group of workers on problems of nutrition at Harvard, having been presented by them at the Harvard Tercentenary Celebration.[223] A practical handbook, which is a brief compendium of new information about the chemistry of the vitamins, units of measurement and tables of the vitamin content of foods, has just been issued by the United States Department of Agriculture. This excellent summary, which will be invaluable to dietitians, is entitled "Vitamin Content of Foods." It was compiled by Esther P. Daniel and Hazel E. Munsell [224] and may be obtained from the Government Printing Office for 15 cents.

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221. Eddy, W. H., and Dalldorf, Gilbert: Avitaminosis, Baltimore, Williams & Wilkins Company, 1937.

222. McCollum, E. V.: Recent Advances in Nutritional Research, J. Michigan M. Soc. **36**:211-227 (April) 1937.

223. Minot, G. R., and others: Symposium on Nutrition and the Deficiency Diseases, New England J. Med. **215**:1147-1166 (Dec. 17) 1936.

224. Daniel, Esther P., and Munsell, Hazel E.: Vitamin Content of Foods, Miscellaneous Publication 275, United States Department of Agriculture, June 1937.

News and Comment

AMERICAN PHYSICIANS' ART ASSOCIATION EXHIBITION

The American Physicians' Art Association, a national organization of members of the medical profession who have ability in the fine arts, will hold its first national exhibition in the San Francisco Museum of Art in June 1938. (The Annual Session of the American Medical Association will be held from June 13 to 17 in the same city.)

The American Physicians' Art Association already has an outstanding membership. There are three classifications for membership: active, associate and contributing.

The first annual exhibition of the association promises to be of unusual interest, with entries to be accepted (after selection by a jury) in the following classes: oils, watercolors, sculpturing, photographs, pastels, etchings, crayon drawings, pen and ink drawings (including cartoons), wood carvings and book bindings. Scientific medical art work will not be accepted. The exhibition is not limited to first showings. All entries must be received by April 1. Any physician interested should communicate at once with the Secretary of the American Physicians' Art Association, Suite 521-536 Flood Building, San Francisco.

Book Reviews

Functionelle Pathologie. By Gustav von Bergmann. Second edition. Price, 25 marks. Pp. 547, with 73 illustrations. Berlin: Julius Springer, 1936.

The new edition of this text will be welcomed with the same enthusiasm which attended the presentation of the first edition in 1932. Von Bergmann approaches disease from the standpoint of functional pathology, proceeding from a general discussion in the first chapter to a specific consideration in succeeding chapters of the important organs—colon, stomach, pancreas, duodenum and biliary tract, followed by a consideration of inflammation, the vitamins and hormones, diabetes, thyroid states and vascular, cardiac and nervous problems. Such an approach to disease is stimulating in at least two ways: First, it integrates for the reader related diseases and passes from the normal to the abnormal function of organs with a clarity of understanding impossible to attain from a study of the isolated disease entities alone. Second, it instills in the student of disease a realization of the importance of knowledge of normal function of tissues, leading to an easy comprehension of the mechanisms of disease.

When possible the author leads to new concepts through a brief historical approach, and although his own researches and views are presented, full consideration is given controversial subjects, for example, the etiology of peptic ulcer. The reader is not denied the opportunity to judge conflicting data. Von Bergmann's investigative interests have been so wide in their scope that, whether the reader is a gastro-enterologist, cardiologist or psychiatrist, he will feel the unusual familiarity and knowledge of the author in his particular field. Free reference is made to the important literature, which is, of course, chiefly continental, and a bibliography is appended to each chapter.

The rarity of adequate texts of this type and the wide interests of the author, who is in active touch with so many branches of the fields covered, will make this book of interest not only to the general reader but as well to those who specialize in the various subdivisions of internal medicine.

Einführung in die pathologische Physiologie. By Max Bürger. Second edition. Price, 24 marks. Pp. 454, with 43 illustrations. Berlin: Julius Springer, 1936.

Twelve years have elapsed since the first edition of this text appeared. The remarkable advances in knowledge of the mechanisms of disease since that time have demanded a complete rewriting, particularly of the important chapters on the vitamins, nutrition and the endocrine glands. The elapse of such a long time makes one wonder why the author has failed to keep this work abreast in a field continually bristling with activity and new thought.

The well known aspects of deranged bodily function are treated under the usual headings, such as respiration, nervous system, metabolism, endocrine glands, blood and heart. Much of the work is sketchily done and at times, particularly in more recent advances originating outside Germany, the newer knowledge is either omitted or only briefly mentioned. This is well shown in the discussion of the pathologic physiology of the parathyroid glands, the relationship of the pituitary glands to carbohydrate metabolism and the mechanisms of the anemias. The work of Houssay is not given its place. Castle's observations leading to the present concepts of the mechanism of macrocytic anemia are considered chiefly outside the section on blood. Apparently the compilation of data on insulin was made too early to include those on protamine insulin.

Briefly, one notes the omission of many data that should rightfully be included in a text of this size and scope.

Synopsis of Diseases of the Heart and Arteries. By George R. Herrmann, M.D., Ph.D., Professor of Clinical Medicine, the University of Texas. Price, $4. Pp. 344, with 91 illustrations. St. Louis: C. V. Mosby Company, 1936.

The author presents this book to fill what he considers a need for a synopsis of diseases of the heart and arteries. In the opinion of the reviewer it is more than a synopsis, running to the length of some textbooks on the subject.

There are a number of inaccuracies in the book, and too many dogmatic statements are made without qualification. This is probably because of the author's original intention of writing the book as a synopsis. For example, on page 277 the statement that aortic stenosis is the rarest of (cardiac) lesions is inaccurate. In addition, many points of practical importance have been omitted. There is also a tendency to give the impression that certain work has been proved to be of value which as yet is not generally accepted. Some chapters, such as those on congenital heart disease, diseases of the great vessels and peripheral vascular diseases, are discussed so briefly as to be of little value. Other chapters, such as the chapter on studies of patients suspected of having heart disease and subsequent chapters in which the various types of heart disease are presented according to etiology, could have been greatly condensed.

The book is therefore too long for a synopsis, it overemphasizes certain subjects and it does not give sufficient space to other important subjects. It offers nothing original or particularly new and probably will be disappointing to those for whom it was intended: "the plodding student and the assiduous conscientious practitioner."

Medical Urology. By Irvin S. Koll, M.D., Attending Urologist, Michael Reese Hospital, Chicago. Price, $5. Pp. 431, with 92 illustrations and 6 colored plates. St. Louis: C. V. Mosby Company, 1937.

The author says that his principal idea in writing this work was to present the subject of urology so as to be of practical value to the general physician and an aid to the medical student. As a general physician, this reviewer wishes to congratulate the author.

The entire volume is so clearly and sanely written that many of the intricacies of the anatomy, physiology and pathology of the genito-urinary organs become readily understandable, as do many of the problems which face the modern urologist. Moreover, since the purpose of the book is to discuss urology for the general reader rather than for the specialist, no space is wasted on too elaborate descriptions of operative technic. On the other hand, appropriately lengthy discussion is given to the less complicated prophylactic, diagnostic and therapeutic procedures in the field, with which every physician should be familiar.

The book is well printed and excellently illustrated. It is of convenient size and shape. It is thoroughly readable. On the whole, it gives every promise of becoming one of those happy texts necessarily fated to have a long and useful existence.

Argentine Archives of the Diseases of the Respiratory System and Tuberculosis, Buenos Aires, Vol. 4, no. 1-4, 1936.

This journal is devoted to the pathology of the respiratory tract and tuberculosis. Each number constitutes a volume of from 100 to 150 pages and is profusely illustrated, containing sections of original work, reports of conferences, proceedings of medical societies, abstracts, bibliographies and reviews of tuberculosis and antituberculosis information. Volume 4 is devoted entirely to bronchography, with chapters by various authors on indications and various technics, and includes a description of the normal anatomy of the respiratory tract as visualized by means of opaque oils. Other chapters discuss bronchography in asthma and chronic bronchitis, carcinoma, atelectasis, bronchiectasis, tuberculosis and tumors of the pleura. The use of opaque oils in determining the etiology of hemoptysis also is discussed. One of the most outstanding articles is that by Drs. Egidio S. Mazzei, Juan A. Aguirre and Miguel E. Jorg, in which they present the subject of the relation of the agenesis of the alveoli to congenital bronchiectasis.

The Harvey Lectures. Delivered Under the Auspices of the Harvey Society of New York, 1935-1936. Series 31. Price, $4. Pp. 255. Baltimore: Williams & Wilkins Company, 1936.

As to be expected, this group of lectures is as instructive and interesting as those of the past. The present group of eight lectures covers an extensive variety of studies: "Proteins and Proteolytic Enzymes" by Max Bergmann, "The Significance of Chimpanzee-Culture for Biological Research" by Robert M. Yerkes, "The Virus Tumors and the Tumor Problem" by Peyton Rous, "Relations Between the Parathyroid, the Hypophysis and the Pancreas" by B. A. Houssay, "The Interrelation of Cerebrum and Cerebellum in the Regulation of Somatic and Autonomic Functions" by John Farquhar Fulton, "The Influenzas of Swine and Man" by Richard E. Shope, "Malignant Cells" by Warren H. Lewis and "The Physiology of the Bronchial Vascular System" by I. de Burgh Daly. The respective subjects are summarized and interpreted by outstanding investigators in their particular fields. Time devoted to reading these lectures will be well spent.

Die Diät- und Insulinbehandlung der Zuckerkrankheit. By Franz Depisch. Price, 4.80 marks. Pp. 136. Vienna: Julius Springer, 1937.

This little volume has a definite place in medical literature. It does not supplant the larger, more distinguished monographs; references are not quoted, and details on controversial aspects of the disease find no place in its pages. Instead, the author gives the student and practitioner a concise introduction to the elements of the modern management of the diabetic patient in a straightforward and easily read style. A discussion of the use of terms and of variations in and regulation of the blood sugar content precedes a brief consideration of the mechanisms of carbohydrate metabolism. Diagnostic pitfalls and the principles of diagnosis are illustrated by case records. Treatment is divided into dietetic handling and management with insulin. Both are clearly developed, but the use of protamine insulin is not included. At the end of each section a number of maxims useful in practice are listed.

The book, to this reviewer, admirably fulfils its purpose.

Textbook of Medicine. By Various Authors. Edited by J. J. Conybeare. Third edition. Price, $7. Pp. 1,027, with 49 illustrations (24 roentgenograms). Baltimore: William Wood & Company, 1936.

The reviewer has reported on previous editions of this book and has always commented favorably. The section on neurology by Walshe seems to be by far the best to be found in any one volume work on practice. The whole text is well written. One may criticize perhaps the ultraconservative point of view adopted at times. Here and there it would have been better to concentrate on what is definitely established to be of value. In the section on renal function, for example, a number of tests which have been generally discarded are still described. In testing gastric secretion the writer always refers to histidine, whereas he probably means histamine. These are minor criticisms, however, and on the whole the book is to be recommended.

Clinical Allergy. By Albert H. Rowe. Price, $8.50. Pp. 812. Philadelphia: Lea & Febiger, 1937.

Rowe deals with the complex subject of allergy in a lucid, readable manner. With his extensive background of interest in the subject, what he has to say is reenforced by personal experience, which is so necessary in giving an adequate presentation to the reader. The general question of allergy is taken up first, and then come special sections on diseases and symptom complexes in which allergy does, or is supposed to, play a part. Every allergist in the reviewer's experience is an enthusiast, and the general physician may wonder whether or not a point is not strained sometimes in bringing forward an allergic explanation of this or that medical phenomenon. The same difficulty is felt when a monograph on endo-

crine disease, vitamin deficiency or any other specialized subject is read. If the general reader, however, preserves his own critical sense, he will find this book an admirable storehouse of information on allergy.

Manifestaciones pulmonares del cuy en el soroche agudo: Estudio anatomo-patológico y consideraciones patogénicas. By Pablo Mori Chavez, M.D. Pp. 59, with 5 illustrations. Lima, Peru: Facultad de Ciencias Medicas de la Universidad Mayor de San Marcos, 1936.

When guinea-pigs were taken from sea level immediately to an altitude of 4,500 or 5,000 meters they showed dyspnea, and a large percentage of them died within from three to five days. At autopsy the lungs showed severe congestion. If death did not occur within the first week, acclimation usually resulted. This adjustment was manifested by the formation of large numbers of new minute blood vessels in the lung. The immediate reaction of guinea-pigs to high altitude indicated marked sensitivity to low oxygen tension, but the capacity for final adjustment was exceptionally good, which is in contrast to the severe pulmonary changes occurring in cats living for a few months at a high altitude. The report contains much of interest. Sixteen photomicrographs of pulmonary tissue are included.

Applied Dietetics. By Frances Stern. Price, $3.50. Pp. 263, with 52 tables. Baltimore: Williams & Wilkins Company, 1937.

Many new books on dietetics have appeared recently, and one naturally looks for some distinctive quality in each. The outstanding character of Miss Stern's work at the Boston Dispensary is well known, and this is reflected in the book, which is one of the few on dietetics that takes up in detail the problem of "getting the diet over to the patient." In addition the usual material on dietetics and food values is well presented in brief form.

Original Papers of Richard Bright on Renal Disease. By A. Arnold Osman, D.S.C., F.R.C.P. Price, $7.25. Pp. 172. London: Oxford University Press, 1937.

This is a beautiful reprinting of the papers by Richard Bright on renal disease. As a result of Bright's presentation on the subject of renal disease, the medical profession first began to differentiate various types of dropsy. The contributions of this truly great man in 1827 were fundamental, and therefore the book is of tremendous historical value. It should be in the library of any physician at all interested in the development of medicine.

Internal Diseases of the Eye and Atlas of Ophthalmoscopy. By Manuel Uribe Troncoso. Price, $15. Pp. 530, with 239 figures (82 color plates). Philadelphia: F. A. Davis Company, 1937.

The reviewer is not an ophthalmologist, but to him this book seems extremely useful. Its main feature is the numerous diagrams and color plates of eyegrounds in conditions both normal and pathologic. The text is brief and seems to be intended mainly to explain the plates.

Lehrbuch der Elektrokardiographie. By Dr. D. Scherf. Price, 16.50 marks. Pp. 241, with 169 illustrations. Wien: Julius Springer, 1937.

This excellently printed and well illustrated monograph covers adequately the subject of clinical electrocardiography and the principal cardiac arrhythmias. Nothing essentially new, however, is added to the material found in the many books on the same subject which have recently appeared.